METHYLPRED

Methylprednisolone (as sodium succinate) powder for injection

alphapharm
A Mylan Company

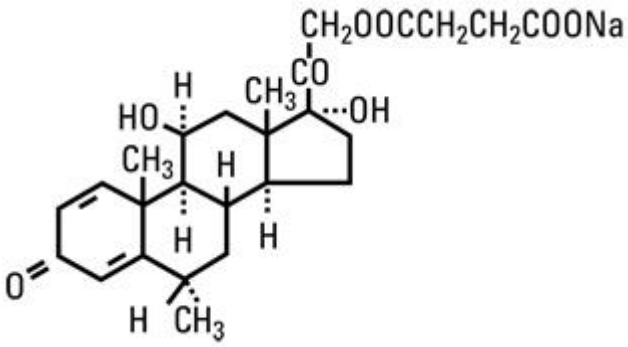
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient : methylprednisolone sodium succinate

Chemical name : Sodium 4-[(11β,17-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-21-yl)oxy]-4-oxobutanoate

Structural formula :



Molecular formula : $C_{26}H_{33}NaO_8$

Molecular weight : 496.53

CAS Registry no. : 2375-03-3

DESCRIPTION

Methylprednisolone sodium succinate USP is a white or nearly white, odourless, hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone. Its melting point is greater than 250°C.

METHYLPRED powder for injection contains methylprednisolone (as methylprednisolone sodium succinate) as the active ingredient. The excipients include sodium phosphate - dibasic anhydrous, sodium phosphate – monobasic anhydrous and lactose (for the 40 mg strength only).

Methylprednisolone sodium succinate is extremely soluble in water so 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.

PHARMACOLOGY

Methylprednisolone is a potent anti-inflammatory steroid. 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 biological activity. The relative potency of METHYLPRED powder for injection 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.

Pharmacokinetics

In vivo, cholinesterases rapidly hydrolyse methylprednisolone sodium succinate to free methylprednisolone. In humans, methylprednisolone forms a weak dissociable bond with albumin and transcortin; approximately 40 to 90% of the drug is bound.

Metabolism of methylprednisolone occurs via the hepatic route and is qualitatively similar to metabolism of cortisol. The major metabolites are 20-beta-hydroxymethylprednisolone and 20-beta-hydroxy-6-alpha-methylprednisolone. The metabolites are mainly excreted in the urine as glucuronides, sulfates and unconjugated compounds. Following intravenous administration of ^{14}C-labelled methylprednisolone, 75% of the total radioactivity was recovered in the urine in 96 hours, 9% in faeces after five days and 20% in the bile.

Peak methylprednisolone plasma levels of approximately 20 microgram/mL are reached after intravenous infusions of 30mg/kg bodyweight administered over 20 minutes, or 1 g over 30 to 60 minutes, while levels of 42 to 47 microgram/mL are measured after an intravenous bolus injection of 40 mg. Peak methylprednisolone plasma levels of 34 microgram/100 mL are measured after 120 minutes following a 40mg intramuscular injection. Lower peak methylprednisolone plasma levels are achieved following intramuscular injection than following intravenous administration. However, the peak plasma value persists for a longer period following intramuscular administration resulting in equivalent quantities of methylprednisolone reaching the plasma independent of the route of administration.

The plasma half-life of methylprednisolone is 2.3 to 4 hours and appears to be independent of the route/pattern of administration. The biological half-life is 12 to 38 hours. The intracellular activity of glucocorticoids results in the marked variation in the plasma and pharmacological half-lives. Pharmacological activity persists after plasma levels are no longer measurable.

The duration of the anti-inflammatory action of glucocorticoids approximately equals the duration of the hypothalamic/pituitary/adrenal (HPA) axis suppression.

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 following conditions.

For intravenous or intramuscular use only.

Endocrine disorders

- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogues 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 analogues 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,
- hypercalcaemia associated with cancer.

Rheumatic disorders

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

- ankylosing spondylitis,
- psoriatic arthritis,
- acute and subacute bursitis,
- synovitis of osteoarthritis,
- acute nonspecific tenosynovitis,
- epicondylitis,
- acute gouty arthritis,
- post-traumatic osteoarthritis,
- rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy).

Collagen disease

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

- systemic lupus erythematosus,
- systemic dermatomyositis (polymyositis),
- acute rheumatic carditis.

Dermatological diseases

- Bullous dermatitis herpetiformis,
- severe psoriasis,
- severe seborrhoeic dermatitis,
- exfoliative dermatitis,
- pemphigus,
- mycosis fungoides,
- severe erythema multiforme (Stevens-Johnson syndrome).

Allergic states

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

- bronchial asthma,
- drug hypersensitivity reactions,
- contact dermatitis,

- urticaria1 transfusion reactions,
- atopic dermatitis,
- serum sickness.
- seasonal or perennial allergic rhinitis,
- acute noninfectious laryngeal oedema (adrenaline is the drug of first choice),

Ophthalmic diseases

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

- allergic corneal marginal ulcers,
- allergic conjunctivitis,
- chorioretinitis,
- anterior segment inflammation,
- herpes zoster ophthalmicus,
- iritis, iridocyclitis,
- diffuse posterior uveitis and choroiditis,
- keratitis,
- optic neuritis,
- sympathetic ophthalmia.

Gastrointestinal diseases

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

- ulcerative colitis (systemic therapy),
- regional enteritis (systemic therapy).

Respiratory diseases

- Symptomatic sarcoidosis,
- berylliosis,
- aspiration pneumonitis,
- Loeffler's syndrome not manageable by other means,
- fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.

Haematologic disorders

- Idiopathic thrombocytopenic purpura in adults (intravenous only, intramuscular administration is contraindicated),

- secondary thrombocytopenia in adults,
- acquired (autoimmune) haemolytic anaemia,
- erythmblastopenia (red blood cell anaemia),
- congenital (erythroid) hypoplastic anaemia.

Neoplastic diseases

For palliative management of;

- leukaemias and lymphomas in adults,
- acute leukaemia of childhood.

Oedematous states

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

Nervous system

- Acute exacerbations of multiple sclerosis.

Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
- Trichinosis with neurological or myocardial involvement.
- METHYLPRED is beneficial as adjunctive therapy in the treatment of acquired immune deficiency syndrome (AIDS) affected patients with moderate to severe *Pneumocystis jiroveci* pneumonia when given within the first 72 hours of initial antipneumocystis treatment.

CONTRAINDICATIONS

Methylprednisolone sodium succinate is contraindicated:

- In patients who have systemic fungal infections
- In patients with known hypersensitivity to methylprednisolone or any component of the formulation.

METHYLPREDNISOLONE SODIUM SUCCINATE IS CONTRAINDICATED FOR INTRATHECAL, EPIDURAL OR LOCAL INJECTION, OR ANY OTHER UNSPECIFIED ROUTE OF ADMINISTRATION.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see PRECAUTIONS, Immunosuppressant Effects/Increased Susceptibility to Infections).

PRECAUTIONS

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. Since complications of treatment with glucocorticoids are dependent on 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.

Immunosuppressant Effects/Increased Susceptibility to Infections

Corticosteroids 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 localise infection when corticosteroids are used. Infections with any pathogen, including viral, bacterial, fungal, protozoal 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. 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.

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.

Similarly, corticosteroids should be used with great care in patients with known or suspected parasitic infections such as Strongyloides (threadworm) infestation, which may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicaemia.

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 immunisation procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

The use of METHYLPRED powder for 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 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.

The use of METHYLPRED in patients with AIDS (as in the adjunctive treatment of *Pneumocystis jiroveci* pneumonia) may be associated with an increased rate of reactivation of tuberculosis. Consideration should therefore be given to the administration of antimycobacterial therapy if corticosteroids are used in this high risk group. Such patients should also be observed for the activation of other latent infections and judicious examinations of sputum/ bronchoalveolar fluid should be made for the presence of other infectious agents.

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

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

Immune System Effects

Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/anaphylactoid reactions (e.g. bronchospasm) 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

There are reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large doses of intravenous METHYLPRED (greater than 0.5 g administered over a period of less than ten 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 (see Adverse Effects, Overdosage, and Dosage and Administration).

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 risk modification and additional cardiac monitoring may need to be considered. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy.

Use of systemic corticosteroid is not recommended in patients with 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.

Corticosteroids should be used with caution in patients with hypertension.

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.

Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy. This effect may be minimised by use of alternate-day therapy.

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

Drug induced secondary adrenocortical insufficiency may be minimised by a 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.

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.

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.

Hepatobiliary Effects

Drug-induced liver injury such as acute hepatitis can result from cyclical pulsed IV methylprednisolone (usually at doses of 1 g/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. Serious hepatotoxicity has been reported.

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

Ocular Effects

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal 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 and may enhance the establishment of secondary ocular infections due to fungi or viruses.

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

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 (see **ADVERSE EFFECTS**). Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions resolve 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 depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Gastrointestinal Effects

High doses of corticosteroids may produce acute pancreatitis.

Corticosteroid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage 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.

Corticosteroids should be used with caution in non-specific ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Nervous System Effects

Use of corticosteroids is not recommended in patients with seizure disorders.

Corticosteroids should be used with caution in patients with myasthenia gravis (see **PRECAUTIONS, Musculoskeletal Effects**).

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 ADVERSE EFFECTS).

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

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 (eg. myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (eg. pancuronium). This acute myopathy is generalised, 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.

Corticosteroids should be used with caution in osteoporosis. Osteoporosis is a common but infrequently recognised adverse effect associated with a long-term use of large doses of glucocorticoid.

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.

Investigations

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.

Injury, Poisoning and Procedural Complications

Systemic corticosteroids are not indicated for, and should therefore not be used to treat traumatic brain injury. A large multicentre randomised study in patients administered corticosteroid therapy after significant head injury revealed an increased risk of mortality in the corticosteroid group compared to the placebo group.

Other

Aspirin and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see INTERACTIONS WITH OTHER MEDICINES, Table 2, NSAIDs).

Benzyl alcohol, which can be found in the alternative recommended diluent, has been reported to be associated with a fatal "Gasping Syndrome" in premature infants (see PRECAUTIONS, Paediatric Use).

Effects on Fertility

Animal studies on the effects of methylprednisolone did not show an adverse impact on fertility in male and female rats treated with methylprednisolone aceponate at subcutaneous doses up to 0.1 mg/kg/day, although there was an increase in the number of non-viable fetuses. Other corticosteroids have been shown to impair fertility and reduce embryonic viability in studies in mice and rats.

Use in Pregnancy: (Category A)

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. There is limited data on the use of methylprednisolone sodium succinate in pregnant women, and animal reproduction studies have not been done. Methylprednisolone sodium succinate should be used in pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Some corticosteroids readily cross the placenta. An increased incidence of low-birth weights in infants born of mothers receiving corticosteroids has been reported.

Infants exposed *in utero* to substantial doses of corticosteroids must be carefully observed and evaluated for signs of adrenal insufficiency.

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

Benzyl alcohol, which can be found in the alternative recommended diluent, can cross the placenta (see **PRECAUTIONS, Paediatric Use**).

Use in Lactation

Corticosteroids are excreted in breast milk.

Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

Paediatric Use

Benzyl alcohol, which can be found in the alternative recommended diluent, is associated with severe adverse effects, including fatal "gasping syndrome", in paediatric patients. The minimum amount of benzyl alcohol at which toxicity may occur is unknown. 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, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

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 a regimen should be restricted to the most urgent indications. Alternate-day glucocorticoid therapy usually prevents or minimises this side effect.

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

High doses of corticosteroids may produce pancreatitis in children.

Use in the Elderly

Caution is recommended with prolonged corticosteroid treatment in the elderly due to a potential increased risk for osteoporosis, as well as increased risk for fluid retention with possible resultant hypertension.

Use in Renal Impairment

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

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.INTERACTIONS WITH OTHER MEDICINES

Methylprednisolone has a wide spectrum of clinical use and is therefore used with numerous concurrent drugs. The interactions tabulated below are of known or likely clinical significance. The need for dosage adjustment of either medication will depend on the clinical situation, the dose regimen prescribed and the observed clinical response. The interactions listed have either a pharmacokinetic or pharmacodynamic basis.

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolised by the CYP3A4 enzyme. CYP3A4 catalyses 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 of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 Inhibitors

Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance, resulting in increased plasma concentrations of corticosteroids. Co-administration of these substances may require titration of corticosteroid dosage to reduce the risk of adverse effects and avoid steroid toxicity.

CYP3A4 Inducers

Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentrations of corticosteroids. Coadministration of these substances may require an increase in corticosteroid dosage to achieve the desired 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 coadministration.

The most common and/or clinically important drug interactions or effects resulting from co-administration of methylprenisolone and examples of CYP3A4 inhibitors, inducers and substrates are provided in Table 1 and 2. Table 1 and 2 should be used in conjunction with the detailed information provided above.

TABLE 1 Examples of CYP3A4 inhibitors, inducers and substrates that interact with SOLU-MEDROL.

	CYP3A4 Inhibitor	**CYP3A4 Inducers**	**CYP3A4 Substrates**
Antibiotics/Antifungal Agents			
Triacetyloleandomycin	**X**		**X**
Erythromycin	**X**		**X**
Ketoconazole	**X**		**X**
Itraconazole	**X**		**X**
Antibiotics/Antitubular Agents			
Rifampin		**X**	
Rifabutin		**X**	
Isoniazid (also see Table 2)	**X**		
Anticonvulsants			
Carbamazepine		**X**	**X**
Phenobartital		**X**	
Phenytoin		**X**	
Antiemetics			
Aprepitant	**X**		**X**
Fosaprepitant	**X**		**X**
Antivirals			
HIV Protease Inhibitors e.g. indinavir and ritonavir	**X**		**X**
Calcium Channel Blocker			
Diltiazem	**X**		**X**
Contraceptives (Oral)			
Ethinylestradiol	**X**		**X**
Norethindrone	**X**		**X**
Grapefruit Juice	**X**		
Immunosuppressants			
Cyclosporin (also see Table 2)	**X**		**X**
Cyclophosphamide			**X**

Tacrolimus			**X**
Macrolide Antibacterial Agents			
Clarithromycin	**X**		**X**
Erthryomycin	**X**		**X**
Troleandomycin	**X**		

Table 2 Drug interactions of known or likely clinical significance

CLASS OF DRUG/DRUG(S) INVOLVED	DRUG(S) AFFECTED/MECHANISM/CLINICAL IMPLICATION
Antibiotic/Antifungal Therapy • Triacetyloleandomycin • Erythromycin • Ketoconazole	CYP3A4 inhibitor Co-administration may result in reduced corticosteroid clearance, enhanced clinical effects and an increased risk of adverse effects of methylprednisolone.
Antibiotics/Antitubular Therapy • Rifampicin	CYP3A4 inducer Increased hepatic clearance which may reduce efficacy of corticosteroid. Dosage adjustment may be required.
Anticholinesterase • Neostigmine • Pyridostigmine	Corticosteroids may reduce the effects of anticholinesterases in myasthenia gravis which may result in precipitation of myasthenic crisis.
Anticoagulants • Oral anticoagulants or heparin	Effect on anticoagulant is variable. Enhanced as well as diminished effects of anticoagulants with co-administration with corticosteroids have been reported. Coagulation indices should be monitored. Adjust dose accordingly to maintain desired anticoagulant effects.
Anticonvulsants • Phenobarbitone • Phenytoin	CYP3A4 inducers Co-administration may increase clearance of methylprednisolone leading to reduced methylprednisolone efficacy. Monitor clinical response. Adjust dose if necessary.
Antidiabetic Drugs • Insulin • Glibenclamide • Metformin	Diabetogenic effects of corticosteroids may impair glucose control of the antidiabetic agents. Monitor glucose levels and adjust dose of antidiabetic therapy if used concurrently with corticosteroids.
All Antihypertensive Agents	Antihypertensive agents are affected with co-administration due to mineralocorticoid effect of corticoid leading to raised blood pressure. May result in partial loss of hypertensive control.
Antitubular agents • Isoniazid	CYP3A4 inhibitor. In addition there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Aromatase inhibitors • Aminoglutethimde	Aminoglutethimde induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Cardioactive drugs • Digoxin and related glycosides	Corticosteroid induced potassium loss (mineralcorticoid effect). Potentiation of digoxin toxicity.
Diuretics • All potassium losing diuretics e.g. frusemide, thiazide • Carbonic anhydrase inhibitors e.g. acetazolamide	Excessive potassium loss may be experienced with concurrent use of corticosteroids and potassium depleting diuretics or carbonic anhydrase inhibitors. There is enhanced toxicity with co-administration and an increased risk of hypokalaemia. Monitor K^+ levels and supplement if necessary.
HIV Protease Inhibitors • e.g. indinavir, ritonavir	Co-administration may increase plasma concentrations of corticosteroids. Corticosteroids may reduce plasma concentrations of HIV-protease inhibitors, by inducing their metabolism.
Immunising Agents • Live vaccine e.g. poliomyelitis, BCG, mumps, measles, rubella, smallpox. • Killed virulent vaccines	Co-administration may result in corticosteroid induced immunosuppression. There may be an increased toxicity from vaccine. Disseminated viral disease may occur (see **CONTRAINDICATIONS** and **PRECAUTIONS**). Co-administration may result in impaired immune

	response and/or reduced response to vaccine (see **CONTRAINDICATIONS** and **PRECAUTIONS**).
Immunosuppressants • Methotrexate • Cyclosporin	Synergistic effect on disease state. 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 likely to occur. May allow reduced dose of corticosteroid. Increased activity of both cyclosporin and corticosteroids with coadministration. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Monitor cyclosporin A levels. Adjust dose as necessary.
Anticholinergics • Neuromuscular blocking agent e.g. pancuronium, vercuronium	Partial reversal of neuromuscular block Acute myopathy has been reported with concurrent use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking agents (see **PRECAUTIONS**). Antagonism of the neuromuscular blocking effects of pancuronium and vercuronium has been reported in patients taking corticosteroids. This reaction may be expected with all competitive neuromuscular blockers.
Potassium depleting agents • Diuretics • Amphotericin B, xanthines or beta 2 agonists	When administered with potassium depleting agents, patients should be observed closely for development of hypokalaemia as there is an increase risk with concurrent use.
Psychotherapeutic • CNS active drugs such as anxiolytics and antipsychotics	Co-administration may potentiate CNS effects of corticosteroid. As the CNS active drug is affected with co-administration, recurrence or poor control of CNS symptoms may result. May require dose adjustment to obtain desired effect.
NSAIDs • Aspirin	There may be increased incidence of gastrointestinal bleeding and ulceration. 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.
Sympathomimetic Agents • Salbutamol	Co-administration leading to increased response to sympathetic agents with resulting increased efficacy and potentially increased toxicity.

ADVERSE EFFECTS

Serious undesirable adverse events are also mentioned under the subheading "PRECAUTIONS".

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 adverse effects are listed below by system organ class

Infections and Infestations

Opportunistic infection, infection[a], peritonitis[g].

Blood and Lymphatic System Disorders

Leucocytosis

Immune System Disorders

Drug hypersensitivity[b], anaphylactic reaction, anaphylactoid reaction.

Endocrine Disorders

Cushingoid, hypopituitarism, steroid withdrawal syndrome, adrenal insufficiency, secondary adrenocortical and pituitary unresponsiveness[c].

Metabolism and Nutrition Disorders

Metabolic acidosis, sodium retention, fluid retention, alkalosis hypokalaemic, dyslipidaemia, glucose tolerance impaired[d] , increased insulin requirement (or oral hypoglycaemic 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), myocardial rupture[e], 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, vomiting, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea.

Hepatobiliary disorders

Hepatitis[f]

Skin and Subcutaneous Tissue Disorders

Angioedema, hirsutism, petechiae, ecchymosis, subcutaneous atrophy, skin atrophy, erythema, hyperhidrosis, skin striae, rash, pruritus, urticarial, acne, skin hyperpigmentation, 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

Abscess sterile, 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, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, suppression of reactions to skin tests[h].

Injury, Poisoning and Procedural Complications

Spinal compression fracture, tendon rupture.

[a] Including masking of infections and latent infections becoming active.
[b] With or without circulatory collapse, cardiac arrest, bronchospasm, or hypertension.
[c] Particularly in times of stress, as in trauma, surgery or illness
[d] Manifestations of latent diabetes mellitus
[e] Following a myocardial infarction.
[f] Hepatitis has been reported with IV administration (see PRECAUTIONS).
[g] Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see PRECAUTIONS).
[h] Not a MedDRA preferred term.

DOSAGE AND ADMINISTRATION

This product is for single use in one patient only.

METHYLPRED 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, if 250 mg or less, may be administered intravenously over at least five minutes. Intramuscular injections (250 mg or less) should be injected slowly into a large muscle. If desired, the medication may be administered in diluted solutions by adding water for injections and withdrawing the indicated dose.

When high dose therapy is desired (i.e. greater than 250 mg), the recommended dose of METHYLPRED sterile powder is 30 mg/kg administered intravenously over at least 30 minutes (see Precautions, Adverse Reactions, and Overdosage.) This dose may be repeated every four to six hours for up to 48 hours.

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

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

For other indications, initial dosage will vary from methylprednisolone 10 to 500 mg depending on the clinical problem being treated. The larger doses may be required for short-term management of severe, acute conditions. The initial dose, up to 250 mg, should be given intravenously over a period of at least five minutes, and if greater than 250 mg, then over at least 30 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 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.

Warning: Benzyl alcohol, which can be found in the alternative recommended diluent, has been reported to be associated with a fatal "Gasping Syndrome" in premature infants (see PRECAUTIONS, Paediatric Use).

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 glucose, determination of blood pressure and bodyweight, and a chest X-ray should be made at regular intervals during prolonged therapy. The state of the upper gastrointestinal tract should be monitored in patients with a history of ulceration or significant dyspepsia.

Pneumocystis Jiroveci Pneumonia

For patients diagnosed with *Pneurnocystis Jiroveci*Pneumonia, presenting with a PaO_2, (arterial oxygen pressure) under 55 mmHg on room air, or where respiratory failure is considered likely, the following regimen should be administered.

Administer METHYLPRED powder for injection 40 mg intravenously every six hours for five to seven days. Upon improvement, oral prednisolone should be instituted with the following tapering regimen:

60 mg (divided four times daily) for two days
50 mg (divided twice daily) for two days
40 mg (divided twice daily) for two days
30 mg (divided twice daily) for two days
20 mg (divided twice daily) for two days
15 mg (divided twice daily) for two days
10 mg (divided twice daily) for two days
5 mg (divided twice daily) for two days, then cease.

Treatment with prednisolone should last a maximum of 21 days or until the end of antipneumocystis therapy.

The following four clinical points should be considered when using adjunctive corticosteroid therapy for AIDS related PCP:

1. Adjunctive corticosteroid therapy should be initiated early (within 72 hours of starting antipneumocystis therapy).

2. The diagnosis of PCP must be confirmed and other pulmonary pathogens ruled out because of the potential for masking symptoms of untreated infections.

3. Antimycobacterial therapy should be initiated along with antipneumocystis therapy in patients with a current positive PPD test or in other high risk patients.

4. Adjunctive corticosteroid therapy should be commenced with the maximum recommended dose. The duration of treatment at this dose should be dependent upon both the severity of the disease and the clinical response to therapy. Following a satisfactory clinical response, a tapering regimen should be instituted. The use of a tapering regimen decreases the potential for relapse upon the discontinuation of corticosteroid therapy.

Multiple sclerosis

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

Recommended administration times

Intravenous use

Recommended intravenous administration times are based on the dose to be administered. Dosages greater than or equal to 500 mg should be given over at least 30 minutes and dosages less than or equal to 250 mg should be given over at least 5 minutes.

Intramuscular use

Intramuscular injections (250 mg or less) should be injected slowly into a large muscle.

Reconstitution of METHYLPRED

METHYLPRED should be reconstituted using bacteriostatic water for injections with benzyl alcohol or sterile water for injections. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

It is recommended that the reconstituted solution of METHYLPRED be used immediately upon preparation.

The volume of diluent recommended and the resulting concentration is as follows:

Product Strength	Recommended Concentration	Volume of Diluent
40mg	40mg/mL	1mL
125mg	62.5mg/mL	2mL
500mg	62.5mg/mL 125mg/mL	8mLs 4mLs
1.0g	62.5mg/mL 125mg/mL	16mLs 8mLs

Preparation of solutions for intravenous infusion

To prepare solutions for intravenous infusion, first prepare the solution for injection as directed above. This solution may then be added to glucose intravenous infusion 5%, sodium chloride intravenous infusion 0.9% or glucose 5% and sodium chloride 0.9% intravenous infusion: the resulting admixtures should be used immediately. This solution is for single use only.

Compatibility and stability

To avoid compatibility and stability problems, whenever possible it is recommended that METHYLPRED be administered separately from other drugs and as either an intravenous injection through an intravenous medication chamber, microburette or as an intravenous ‘piggy-back’ solution. The intravenous compatibility and stability of methylprednisolone sodium succinate, either alone in solution or in admixtures with other drugs, is dependent on pH, concentration, time, temperature and the ability of methylprednisolone to solubilise itself.

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.

OVERDOSAGE

Symptoms

Reports of acute toxicity and metabolic disturbances with glucocorticoids are rare but do occur. There is no clinical syndrome of acute overdosage with METHYLPRED powder for injection. Acute overdose may possibly aggravate pre-existing disease states, e.g. ulceration of the gastrointestinal tract, electrolyte disturbances, infections, diabetes and oedema. Repeated high doses of methylprednisolone have caused hepatic necrosis and

an increase in amylase. Bradyarrhythmias, ventricular arrhythmias and cardiac arrest have been observed in cases of intravenous administration of high doses of methylprednisolone.

Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state. The possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time.

Treatment

In the event of an overdose, treatment is symptomatic and supportive, including respiratory and cardiovascular function. In chronic toxicity, fluids and electrolytes should be monitored closely. Serum levels are not clinically useful

Immediately telephone the Poisons Information Centre for advice on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

METHYLPRED powder for injection is available in 4 strengths; 40 mg, 125 mg, 500 mg and 1.0 g.

All presentations are a white to off white lyophilized plug or powder.

40 mg: Packs of 1- and 5 vials.

125 mg: Packs of 1 and 5- vials.

500 mg: Packs of 1 and 5- vials.

1.0 g: Packs of 1 and 5- vials.

Not all strengths, pack sizes and/or types may be available.

Store below 25°C. Protect from light.

When reconstituted using bacteriostatic water for injections with benzyl alcohol, or sterile water for injections, the resulting solution should be used immediately. Discard any unused portion.

NAME AND ADDRESS OF SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

S4 (Prescription only medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

METHYLPRED 40 mg: 08/04/2009

METHYLPRED 125 mg: 08/04/2009

METHYLPRED 500 mg: 08/04/2009

METHYLPRED 1 g: 28/10/2010

DATE OF MOST RECENT AMENDMENT: 5th August 2016

Methylpred_pi\Jun16/00