METHYLPREDNISOLONE SODIUM SUCCINATE POWDER FOR INJECTION

Presentation
Methyprednisolone Sodium Succinate Powder for Injection is a sterile lyophilised powder for injection containing 500 mg or 1000 mg of Methyprednisolone as the sodium succinate. It also contains 6.4 mg sodium acid phosphate and 69.8 mg sodium phosphate or 12.8 mg sodium acid phosphate and 139.6 mg sodium phosphate.

Uses

Actions
Methyprednisolone in the form of methyprednisolone sodium succinate is a potent synthetic corticosteroid. Its anti-inflammatory potency is greater than prednisolone in the ratio of 5 to 4. It has only minimal mineralocorticoid properties and has less tendency than prednisolone to induce sodium and water retention. It influences carbohydrate, protein, fat and purine metabolism, electrolyte and water balance, and the functional capacities of the cardiovascular system, the kidney, the skeletal muscle, nervous system and other organs and tissues. It exerts a suppressive effect on the immune response.

Pharmacokinetics
Methyprednisolone sodium succinate for injection, is rapidly and extensively hydrolysed in vivo by cholinesterases to free methyprednisolone.

Indications
Methyprednisolone sodium succinate may be used in conditions in which a rapid, intense glucocorticoid effect is required.

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

Collagen Diseases (Immune and Complex Diseases)
During an exacerbation or as maintenance therapy in selected cases of:
• systemic lupus erythematosus (and lupus nephritis)
• acute rheumatic carditis
• systemic dermatomyositis (polymyositis)
polyarteritis nodosa
Good pasture's syndrome

**Dermatologic Diseases**
- Pemphigus
- severe erythema multiforme (Stevens-Johnson syndrome)
- exfoliative dermatitis
- bullous dermatitis herpetiformis
- severe seborrhoeic dermatitis
- severe psoriasis
- mycosis fungoides

**Allergic States**
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
- bronchial asthma
- contact dermatitis
- atopic dermatitis
- serum sickness
- seasonal or perennial allergic rhinitis
- drug hypersensitivity reactions
- urticarial transfusion reactions
- acute non-infectious laryngeal oedema (epinephrine is the drug of first choice)
- Severe hypersensitivity reactions. In life threatening situations such as anaphylactic reactions, adrenaline should be administered first to achieve an immediate haemodynamic effect. This may be followed by an intravenous injection of methylprednisolone sodium succinate and other accepted procedures.

**Ophthalmic Diseases**
Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
- herpes zoster ophthalmicus
- iritis, iridocyclitis
- chorioretinitis
- diffuse posterior uveitis and choroiditis
- optic neuritis
- sympathetic ophthalmitis
- anterior segment inflammation
- allergic conjunctivitis
- allergic corneal marginal ulcers
- keratitis

**Gastrointestinal Diseases**
To tide the patient over a critical period of the disease in –
- ulcerative colitis (systemic therapy) or Crohn’s disease
- regional enteritis (systemic therapy)

**Respiratory Diseases**
- symptomatic sarcoidosis
- berylliosis
- fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate anti-tuberculous chemotherapy
- Loeffler's Syndrome not manageable by other means
- aspiration pneumonitis
- Status asthmaticus
- Methylprednisolone is beneficial as adjunctive therapy in the treatment of Aids patients with moderate to severe pneumocystis carinii pneumonia when given in the first 72 hours of initial anti-pneumocystis treatment. Due to the increased rate of reactivation of tuberculosis in Aids patients, consideration should be given to the administration of anti-mycobacteria therapy if corticosteroids are used in this high risk group. The patient should also be observed for activation of other latent infections.
Haematologic Disorders
- acquired (autoimmune) haemolytic anaemia
- idiopathic thrombocytopenia purpura in adults (IV only; IM administration is contraindicated)
- secondary thrombocytopenia in adults
- erythroblastopenia (RBC anaemia)
- congenital (erythroid) hypoplastic anaemia

Neoplastic Diseases
For palliative management of:
- leukaemias and lymphomas in adults
- acute leukaemia of childhood

Terminal Cancer
- To improve quality of life in patients with terminal cancer.

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
- Cerebral oedema from tumour - primary or metastatic and/or associated with surgical or radiation therapy.
- Acute exacerbations of multiple sclerosis.
- Acute spinal chord injury. The treatment should begin within eight hours of injury.

Cardiovascular Conditions
- Shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present. (Hydrocortisone is generally the drug of choice. When mineralocorticoid activity is undesirable, methylprednisolone may be preferred.)

Although there are no well controlled (double-blind placebo) clinical trials, data from experimental animal models indicate that methylprednisolone may be useful in haemorrhagic, traumatic and surgical shock in which standard therapy (e.g. fluid replacement, etc.) has not been effective.

The adjunctive use of intravenous methylprednisolone sodium succinate in severe shock may assist in achieving haemodynamic restoration. Corticosteroid therapy should not replace standard methods of combating shock.

Organ Transplantation
- Suppression of graft rejection reactions following transplantation, as part of a treatment regime.

Miscellaneous
- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
- Trichinosis with neurologic or myocardial involvement.
- Prevention of nausea and vomiting associated with cancer chemotherapy.

NB: Methylprednisolone sodium succinate should principally be used for short-term emergency treatment.

Dosage and Administration
After reconstitution, Methylprednisolone Sodium Succinate for Injection may be given by intravenous or intramuscular injection or by intravenous infusion (intermittent or continuous). For initial emergency use, direct IV push or intermittent infusion is the preferred method. Methylprednisolone Sodium Succinate for Injection is not indicated for intrathecal, epidural or local injection.

As adjunctive therapy in life threatening conditions (e.g. shock states) the recommended dose of Methylprednisolone is 30 milligrams per kg of methylprednisolone sodium succinate, given IV over a period of at least 30 minutes. This dose may be repeated every 4 to 6 hours for up to 48 hours.
Pulse dosing for corticosteroid responsive diseases in exacerbation and/or unresponsive to standard therapy (eg. lupus nephritis, rheumatoid arthritis, etc.). Suggested schedules -

- Rheumatic disorders: 1 gm/day for one, two, three or four days IV or 1 gm/month for six months IV.
- Systemic lupus erythematosus: 1 gm/day for three days IV.
- Multiple sclerosis: 1 gm/day for three days IV or 1 gm/day for five days IV.
- Oedematous states e.g. glomerulonephritis, lupus nephritis: 30 mg/kg every other day for four days IV or 1 gm/day for three, five or seven days IV.

The regimen should be administered over at least 30 minutes, and may be repeated if improvement has not occurred within a week after therapy or as patient's condition dictates.

**Terminal Cancer – Quality of Life**

Prospective controlled studies have shown that Methylprednisolone 125 milligrams administered intravenously daily for up to eight weeks, significantly improves quality of life in patients with terminal cancer.

**Prevention of nausea and vomiting associated with cancer chemotherapy.**

Suggested schedules: Mild to moderately emetogenic chemotherapy: Administer Methylprednisolone 250 milligrams IV over at least five minutes one hour before chemotherapy, at the initiation of chemotherapy, and at the time of discharge.

A chlorinated phenothiazine may also be used with the first dose of Methylprednisolone for increased effect.

Severely emetogenic chemotherapy: Administer Methylprednisolone 250 milligrams IV over at least 5 minutes with appropriate doses of metoclopamide or a butyrophenone one hour before chemotherapy, then Methylprednisolone 250 milligrams IV at the initiation of chemotherapy and at time of discharge.

**Acute Spinal Chord Injury**

Administer intravenously 30 milligrams per kilogram of body weight in a bolus dose over a 15 minute period, followed by a 45 minute pause, and then a continuous infusion of 5.4 mg/kg per hour for 23 hours. There should be a separate intravenous site for the infusion pump. The treatment should begin within eight hours of injury.

**Pneumocystis carinii pneumonia in patients with AIDS**

A number of dosage schedules have been used. One approach is to administer 40 milligrams Methylprednisolone every 6 to 12 hours with gradual tapering over a maximum of 21 days or until the end of the pneumocystis therapy. Therapy should be started within 72 hours of initial anti-pneumocystis treatment.

**Other**

In other indications, initial dosage will vary from 10 to 500 milligrams depending on the clinical problem being treated. Larger doses may be required for short term management of severe, acute conditions. The initial dose, up to 250 milligrams, should be given intravenously over a period of at least five minutes and if greater than 250 milligrams, should be given over at least 30 minutes. It should not be less than 0.5 milligrams per kg every 24 hours. Subsequent doses may be given intravenously or intra-muscularly at intervals dictated by the patient's response and clinical condition. Corticosteroid therapy is an adjunct to, and not a 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 milligrams per kg every 24 hours.

Methylprednisolone sodium succinate may be administered by intravenous or intra-muscular 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.

**Reconstitution**

Reconstitute with either Water for Injections BP (for IV injection) or Bacteriostatic Water for Injection USP (for IM or IV injection) as shown in the following table:
Amount of Methylprednisolone present as the sodium succinate | Volume of diluent | Final concentration
--- | --- | ---
500 milligrams | 7.8 mL | 62.5 mg/mL
1000 milligrams | 15.6 mL | 62.5 mg/mL

(Note: Do not use doses of less than 125 milligrams as accurate administration cannot be guaranteed).

When reconstituted with Bacteriostatic Water for Injection, the resulting solution may be stored for up to 48 hours at room temperature. It is recommended however, that reconstituted solutions be stored under refrigeration and used as soon as practical in order to avoid microbial contamination. Solutions with a slight haze should be discarded.

When reconstituted with Water for Injections, the solution should be used immediately and the unused portion discarded.

**Intravenous Infusions**

The reconstituted solution may be further diluted with 0.9% Sodium Chloride Injection, Glucose Intravenous Infusion 5% or Sodium Chloride 0.9% and Glucose 5% Intravenous Infusion to a concentration of 1 mg/mL for intravenous infusion. The potency of Methylprednisolone as the sodium succinate at this dilution is retained for up to 48 hours at room temperature under fluorescent light. However, it is recommended that, as with all intravenous admixtures, dilution should be made just prior to administration and the resulting solution used within 24 hours. Unused solution should be discarded.

To avoid compatibility and stability problems, it is recommended that Methylprednisolone Sodium Succinate Powder for Injection be administered separately from other drugs, by IV push through an IV medication chamber.

**Contraindications**

- Systematic infections unless specific anti-infective therapy is given
- Live virus immunisation
- Hypersensitivity to any ingredient of the medication

**Warnings and Precautions**

**General Precautions**

Caution is necessary when oral corticosteroids are used in patients with the following conditions and frequent monitoring is necessary:
- Hypertension
- Hypothyroidism
- Congestive Heart failure or recent myocardial infarction
- Liver failure
- Renal insufficiency
- Diabetes mellitus or in those with a family history of diabetes
- Osteoporosis
- Glaucoma
- Patients with a history of severe affective disorders particularly of steroid induced psychoses
- Epilepsy and/or seizure disorder
- Peptic ulceration
- Previous steroid myopathy
- Tuberculosis
- Patients with myasthenia gravis receiving anticholinesterase therapy since corticosteroid use may decrease plasma anticholinesterase activity
- Patients with thromboembolic disorders
- Patients with Duchenne’s muscular dystrophy since transient rhabdomyolysis and myoglobinuria have been reported following strenuous physical activity
- Patients with Cushing’s disease
Short term administration of corticosteroids and short courses of high dose intermittent Methylprednisolone are unlikely to produce harmful effects provided the drug is given at the recommended rate of administration. However, if used for longer than 48 to 72 hours continuously, severe endocrinological and cardiovascular side effects can occur. Secondary adrenocortical insufficiency leading to adrenal atrophy and generalised protein depletion have been reported.

High dose intravenous injection must be administered in diluted form and given slowly over at least 30 minutes to avoid the possibility of cardiovascular toxicity. Occasional reports of cardiac arrhythmia, circulatory collapse or cardiac arrest have been reported following high doses given over a very short period of time (greater than 500 milligrams over a period of less than 10 minutes). Monitoring facilities should be available at all times when high dose intravenous therapy is used. 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.

Intramuscular injection repeated at the same site may cause subcutaneous atrophy and should be avoided. Deep injection into the gluteal muscle is recommended.

Methylprednisolone Sodium Succinate for Injection is not indicated for intrathecal, epidural or local injection.

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

Recent studies do not establish the efficacy of Methylprednisolone in septic shock, and suggest that increased mortality may occur in some subgroups at higher risk (i.e. elevated creatinine greater than 2.0 milligrams % or secondary infections).

Use with caution in patients with ulcerative colitis if there is a probability of impending perforation, abscess or other infection; fresh anastomoses; peptic ulcer; hypertension; myasthenia gravis; diabetes; glaucoma; previous myopathy, diverticulitis, renal insufficiency, osteoporosis. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. 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 (see also Interactions).

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 quadriaparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

The use of Methylprednisolone Sodium Succinate 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.

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

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

Gastric irritation may occur in patients with cerebral oedema induced by trauma, and prophylactic antacids may be advisable.

Glucocorticoids, especially in high doses, increase susceptibility to and mask the symptoms of infection.
Sodium retention, hypokalaemia, oedema or hypertension may occur in patients receiving glucocorticoids especially in high doses for long periods.

Glucocorticoids may decrease glucose tolerance, producing hyperglycaemia and aggravate or precipitate diabetes mellitus particularly in predisposed patients. The normal precautions in the use of systemic corticosteroids should be observed.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a 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.

**Adrenocortical Insufficiency**

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 therapy.

Symptoms of adrenal insufficiency include: malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

During prolonged courses of corticosteroid therapy sodium intake may need to be reduced and calcium and potassium supplements may be necessary. Monitoring of fluid intake and output and daily weight records may give an early warning of fluid retention.

Acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly, therefore withdrawal of corticosteroids should always be gradual. A degree of adrenal insufficiency may persist for 6 to 12 months; therefore in any situation of stress occurring during that period steroid therapy may need to be reinstituted. Since mineralocorticoid secretion may be impaired treatment with salt and/or a mineralocorticoid may also be needed.

During prolonged therapy, any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage.

If used to treat adrenal insufficiency a mineralocorticoid drug will also be necessary as Methylprednisolone has only minimal mineralocorticoid action.

**Anti-inflammatory/Immunosuppressive effects and Infection**

Suppression of the inflammatory response and immune function increases susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognized when corticosteroids are used. The immunosuppressive effects of glucocorticoids may result in activation of latent infection or exacerbation of intercurrent infections.

Chickenpox is of particular concern since this may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunization is recommended for non-immune patients who do come into contact with chickenpox. If a diagnosis of chickenpox is confirmed the illness warrants specialist care and urgent treatment.

Live vaccines are contra-indicated in individuals on high doses of corticosteroids and should be postponed until at least 3 months after stopping corticosteroid therapy.

**Ocular Effects**

Prolonged use of corticosteroids may produce 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. Prolonged use of corticosteroids may also enhance the establishment of secondary ocular infections due to fungi or viruses.

Corticosteroids should only be initiated in patients with ocular herpes simplex with appropriate viral cover by ophthalmologists because of the risk of corneal scarring, loss of vision and corneal perforation.
Psychiatric effects
Patients and/or careers should be warned that potentially severe psychiatric reactions may occur. 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. Patients and/or carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.

Particular care is required when considering the use of corticosteroids in patients with existing or previous history of severe affective disorders.

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.

Carcinogenesis, mutagenesis, impairment of fertility
There is no evidence that corticosteroids are carcinogenic, mutagenic, or impair fertility.

Use in children
Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible and therefore long-term administration of pharmacological doses should be avoided. If prolonged therapy is necessary, treatment should be limited to the minimum suppression of the hypothalamo-pituitary adrenal axis and growth retardation, the growth and development of infants and children should be closely monitored. Treatment should be administered where possible as a single dose on alternate days.

Children are at special risk from raised intracranial pressure.

In premature neonates it may be preferable to use non-preserved Water for Injections in the reconstitution process as Benzyl Alcohol has been associated with the “gasping syndrome”. In this case, the product will not contain a preservative and must be used as soon as practicable to avoid microbial contamination.

Use in children may cause growth retardation in infancy, childhood and adolescence.

Use in the elderly
Long-term use in the elderly should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age, especially osteoporosis, diabetes, hypertension, hypokalaemia, susceptibility to infection and thinning of the skin. Close medical supervision is required to avoid life threatening reactions.

Pregnancy and Lactation
Use in pregnancy. In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations). These findings do not seem relevant to humans. Reduced placental and birth weight have been recorded in animals and humans after long-term treatment. Since the possibility of suppression of the adrenal cortex in the new born baby after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the foetus when prescribing corticosteroids.

Use in lactation. Corticosteroids may be distributed into milk and thus could suppress growth or cause other adverse effects in the infants. Women taking pharmacologic doses of corticosteroids are advised not to nurse their infants.

Effects on ability to drive and use machines
Methylprednisolone Sodium Succinate Powder for Injection is likely to produce minor or moderate adverse effects, which may impair the patient's ability to concentrate and react and therefore may constitute a risk in the ability to drive and use machines.

Adverse Effects
If used for short-term therapy the incidence of adverse reactions to Methylprednisolone sodium succinate therapy is rare. High dose therapy may be associated with reactions common to corticosteroids such as:
**Body as a whole**
Leucocytosis, hypersensitivity including anaphylaxis, thromboembolism, fatigue, malaise.

**Gastrointestinal**
Dyspepsia, nausea, peptic ulceration with perforation and haemorrhage, Abdominal distension, abdominal pain, increased appetite which may result in oesophageal ulceration or candidiasis, weight gain, diarrhoea, oesophagitis, ulceration, oesophageal candidiasis, acute pancreatitis, gastric haemorrhage and perforation of the bowel. Nausea, vomiting and bad taste may occur with repeated administration.

**Musculoskeletal**
Muscle weakness steroid myopathy, aseptic necrosis, osteoporosis, long bone or vertebral and pathologic fractures, avascular osteonecrosis, tendon rupture, myalgia. particularly of the Archillies tendon.

**Cardiovascular**
Sodium and water retention, hypertension, hypotension, potassium loss, hypokalaemic alkalosis, cardiac arrhythmias, congestive heart failure.

**Metabolic/Nutritional**
Sodium and water retention, hypokalaemic alkalosis, potassium loss, negative nitrogen and calcium balance.

**Skin**
Impaired wound healing, hirsutism, skin atrophy, bruising, striae, petechiae, telangiectasia, acne, increased sweating, may suppress reactions to skin tests, pruritis, rash and urticaria. ecchymotic manifestations, hyperpigmentation, hypopigmentation, thin fragile skin.

**Endocrine**
Supression of the hypothalamo-pituitary adrenal axis particularly in times of stress as in trauma surgery or illness, growth suppression in infancy, childhood and adolescence, Menstrual irregularity and amenorrhoea, Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, manifestation of latent diabetes mellitus, increased appetite. negative nitrogen balance, suppression of growth in children, suppression of pituitary-adrenal axis.

**Nervous system**
Euphoria, psychological dependence, depression, insomnia, dizziness, headache, vertigo, raised intracranial pressure with papilloedema hypertension in children usually after treatment withdrawal. Aggravation of schizophrenia. Aggravation of epilepsy suicidal ideation, mania, delusions, hallucinations, irritability, anxiety, insomnia and cognitive dysfunction. In adults the frequency of severe psychiatric reactions has been estimated to be 5-6%. pseudotumor cerebri, seizures, increased intracranial pressure, psychic derangements.

Eye DisordersIncreased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or sclera thinning, exacerbation of ophthalmic viral or fungal disease, exophthalmos.

**Anti-inflammatory and Immunosuppressive effects**
Increased susceptibility to and severity of infections with suppression of clinical symptoms and signs. Opportunistic infections, recurrence of dormant tuberculosis.

**Withdrawal symptoms**
Too rapid a reduction of corticosteroids following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. A steroid withdrawal syndrome seemingly unrelated to adrenocortical insufficiency may occur and include symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, weight loss, and/or hypotension.
Interactions
Methylprednisolone has a wide spectrum of clinical use and is therefore used with numerous concurrent drugs.

Potassium depleting diuretics may exacerbate the potassium wasting effects of Methylprednisolone.

*Hepatic microsomal enzyme inducers*
Medicines that induce hepatic enzyme cytochrome P-450 isozyme 3A4 such as Phenobarbital, phenytoin, rifampicin, rifabutin, carbamazepine, primidone and aminogluthimide may reduce the therapeutic efficacy of corticosteroids by increasing the rate of metabolism.

*Hepatic microsomal enzyme inhibitors*
Medicines that inhibit hepatic enzyme cytochrome P-450 isozyme 3A4 such as ketoconazole, ciclosporin or ritonavir may decrease glucocorticoid clearance. A reduction in corticosteroid dose may be needed to reduce the risk of adverse effects.

*Antidiabetic Agents*
Corticosteroids may increase blood glucose levels. Patients may need dosage adjustment of any concurrent antidiabetic therapy.

*Non-steroidal anti-inflammatory drugs (NSAIDs)*
Concomitant administration may increase the risk of GI ulceration. Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypothyrombinaemia. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Patients should be observed closely for adverse effects of either medicine.

*Anticoagulants*
Response to anticoagulants may be reduced or less often enhanced by corticosteroids. Close monitoring of the INR or prothrombin time is recommended.

*Antifungals*
The risk of hypokalaemia may be increased with amphotericin.

*Cardiac glycosides*
There is a risk of toxicity if hypokalaemia occurs due to corticosteroid treatment.

*Mifepristone*
The effect of corticosteroids may be reduced for 3-4 days after mifepristone.

*Vaccines*
Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

*Oestrogens*
Oestrogens may potentiate the effects of glucocorticoids. The dose of corticosteroid may need to be adjusted if oestrogen therapy is commenced or stopped.

*Somatropin*
The growth promoting effect may be inhibited.

*Sympathomimetics*
There is an increased risk of hypokalaemia if high doses of corticosteroids are given with high doses of salbutamol, salmeterol, terbutaline or formoterol.

*Diuretics*
Excessive potassium loss may be experienced if glucocorticoids and potassium-depleting diuretics (such as frusemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide) are given together. Serum potassium levels should be closely monitored during treatment.
**Antacids**

Concurrent use of antacids may decrease absorption of corticosteroids – efficacy may be decreased sufficiently to require dosage adjustments in patients receiving small doses of corticosteroids.

Vaccinations (see Warnings and Precautions).

The interactions summarised in the table 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 pharmacokinetic or pharmacodynamic basis.

<table>
<thead>
<tr>
<th>CLASS OF DRUG</th>
<th>DRUG(S) INVOLVED</th>
<th>DRUG(S) EFFECTED</th>
<th>MECHANISM</th>
<th>CLINICAL IMPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic/Antifungal therapy</td>
<td>Troleandomycin, Erythromycin, Ketoconazole</td>
<td>Methylprednisolone</td>
<td>Enzyme inhibition: Reduced MP elimination</td>
<td>Enhanced clinical effects and side effects of methylprednisolone</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>Methylprednisolone</td>
<td>Enzyme induction, increased clearance</td>
<td>May reduce efficacy; dosage adjustment may be required</td>
</tr>
<tr>
<td>Anticholinesterase</td>
<td>Neostigmine, pyridostigmine</td>
<td>Anticholinesterase</td>
<td></td>
<td>Precipitation of myasthenic crisis.</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Oral anticoagulants or heparin</td>
<td>Anticoagulant</td>
<td></td>
<td>Increased or decrease clotting. Monitor response. Adjust dose</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>e.g. Phenobarbitone, Phenytoin</td>
<td>Methylprednisolone</td>
<td>Enzyme induction: increased clearance of methylprednisolone</td>
<td>May reduce methylprednisolone efficacy. Monitor clinical response. Adjust dose if necessary</td>
</tr>
<tr>
<td>Antidiabetic Drugs</td>
<td>e.g. Insulin, glibenclamide, metformin</td>
<td>Antidiabetic</td>
<td>Diabetogenic effects of corticosteroid</td>
<td>May impair glucose control. Monitor glucose levels and adjust dose of antiabetic therapy.</td>
</tr>
<tr>
<td>Antihypertensive Agents</td>
<td>All Antihypertensives</td>
<td>Antihypertensive</td>
<td>Mineralocorticoid effect of corticosteroid leading to raised blood pressure</td>
<td>May result in partial loss of hypertensive control</td>
</tr>
<tr>
<td>Cardioactive drugs</td>
<td>Digoxin and related glycosides</td>
<td>Digoxin</td>
<td>Corticosteroid induced potassium loss (mineralocorticoid effect)</td>
<td>Potentiation of digoxin toxicity</td>
</tr>
<tr>
<td>Diuretics</td>
<td>All potassium losing diuretics e.g. frusemide</td>
<td></td>
<td>Potassium loss</td>
<td>Enhanced toxicity. Monitor K+ levels and supplement if necessary</td>
</tr>
<tr>
<td>Immunising Agents</td>
<td>Live vaccine: poliomyelitis, BCG, mumps, measles, rubella, smallpox</td>
<td>Vaccine</td>
<td>Corticosteroid induced immunosuppression</td>
<td>May see increase toxicity from vaccine. Disseminated viral disease may occur.</td>
</tr>
<tr>
<td></td>
<td>Killed Virulent Vaccines</td>
<td>Vaccine</td>
<td>Impaired immune response</td>
<td>Reduced response to vaccine</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Methotrexate</td>
<td>Methylprednisolone</td>
<td>Synergistic effect on disease state</td>
<td>May allow reduced dose of corticosteroid</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>-------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Cyclosporin (CYA)</td>
<td>Both</td>
<td>Mutual inhibition of metabolism</td>
<td>Monitor cyclosporin A levels. Adjust dose as necessary</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuromuscular Blocking Agents</th>
<th>Pancuronium</th>
<th>Pancuronium</th>
<th>Partial reversal of neuromuscular block</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Psychotherapeutic</th>
<th>Anxiolytics Antipsychotics</th>
<th>CNS active drug</th>
<th>CNS effects of corticosteroid</th>
<th>Recurrence or poor control of CNS symptoms. May require dose adjustment</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Salicylates</th>
<th>Salicylate</th>
<th>Increased clearance and decreased plasma level</th>
<th>Apparent decrease in salicylate efficacy or salicylate toxicity on reduction of corticosteroid dose</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sympathomimetic Agents</th>
<th>e.g. Salbutamol</th>
<th>Increased response to sympathetic agents</th>
<th>Increased efficacy and potentially increased toxicity</th>
</tr>
</thead>
</table>

### Overdosage
There is no specific antidote for a methylprednisolone overdose. If massive doses are inadvertently given, observe parameters of adrenal function over a period of several days and treat symptomatically. Methylprednisolone is significantly removed by haemodialysis.

In case of overdose, immediately contact the Poisons Information Centre for advice, in New Zealand call 0800 764 766).

### Pharmaceutical precautions

**Special Precautions for Storage**
Store below 25°C. Protect from light.

**Incompatibilities**
To avoid compatibility and stability problems, it is recommended that Methylprednisolone Sodium Succinate be administered separately from other drugs, by IV push through an IV medication chamber.

### Package quantities

<table>
<thead>
<tr>
<th>500 mg per 20 ml</th>
<th>1 vial per pack</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 mg per 30 mL</td>
<td>1 vial per pack</td>
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</tbody>
</table>

### Medicine classification
Prescription Medicine.

### Name and address
Hospira NZ Limited
23 Haining Street
Te Aro
Wellington
New Zealand

### Date of preparation
20 April 2012