Methylprednisolone Alphapharm Powder for Injection

Methylprednisolone (as sodium succinate)

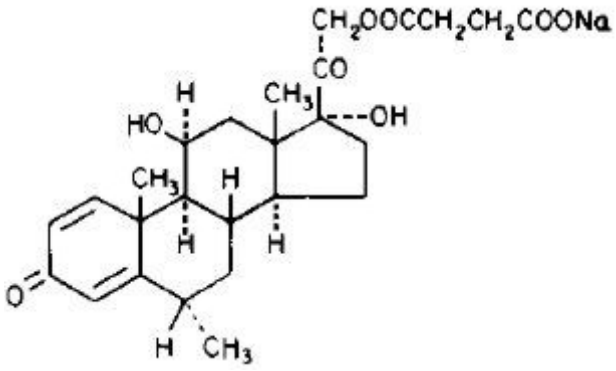
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Methylprednisolone sodium succinate

Chemical name: Pregna-1,4-diene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-6-methyl-,monosodium salt,(6α,11β)

Structural formula:



Molecular formula: $C_{26}H_{33}NaO_8$ Molecular weight: 496.53

CAS Registry No: 2375-03-3

DESCRIPTION

Methylprednisolone Alphapharm contains methylprednisolone sodium succinate, a synthetic glucocorticoid. It occurs as 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.

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.

Methylprednisolone Alphapharm 40 mg, powder for injection (IM-IV) contains the active ingredient, methylprednisolone. It also contains the following excipients: sodium phosphate monobasic anhydrous, sodium phosphate dibasic anhydrous, sodium hydroxide and lactose anhydrous. It is intended for intramuscular or intravenous administration.

Methylprednisolone Alphapharm 500 mg and 1 g, powder for injection (IV) contain the active ingredient, methylprednisolone. They also contain the following excipients: sodium phosphate monobasic anhydrous, sodium phosphate dibasic anhydrous and sodium hydroxide, and are indicated for intravenous administration only.

PHARMACOLOGY

Pharmacodynamics

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

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 biologically. The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to one. This has shown to be consistent with the relative oral potency of methylprednisolone and hydrocortisone.

Pharmacokinetics

In vivo, cholinesterases rapidly hydrolyse methylprednisolone sodium succinate to free methylprednisolone. In man, 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, sulphates and unconjugated compounds. Following intravenous (IV) administration of ^{14}C labelled methylprednisolone, 75% of the total radioactivity was recovered in the urine in 96 hours, 9% in faeces after 5 days and 20% in the bile.

Peak methylprednisolone plasma levels of approximately 20 μg/mL are reached after IV infusions of 30 mg/kg body weight administered over 20 minutes, or 1 g over 30 to 60 minutes, whilst levels of 42-47 μg/mL are measured after an IV bolus injection of 40 mg. Peak methylprednisolone plasma levels of 34 μg/100 mL are measured after 120 minutes following a 40 mg intramuscular (IM) injection. Lower peak methylprednisolone plasma levels are achieved following IM injection than IV administration. However, the peak plasma value persists for a longer period following IM 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 36 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 hypothalmic-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 condition, Methylprednisolone Alphapharm is indicated only 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 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.

2. *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
- Epicondylitis
- Synovitis of osteoarthritis
- Acute gouty arthritis
- Acute nonspecific tenosynovitis
- Post-traumatic osteoarthritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

3. ***Collagen Disease*****:** During an exacerbation or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus
- Systemic dermatomyositis (polymyositis)
- Acute rheumatic carditis.

4. ***Dermatological Diseases*****:**

- Bullous dermatitis herpetiformis
- Pemphigus
- Severe psoriasis
- Severe seborrhoeic dermatitis
- Exfoliative dermatitis
- Mycosis fungoides
- Severe erythema multiforme (Stevens-Johnson Syndrome).

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
- Serum sickness
- Seasonal or perennial allergic rhinitis
- Acute noninfectious laryngeal oedema (adrenaline is the drug of first choice)

6. ***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.

7. *Gastrointestinal Diseases*: To tide the patient over a critical period of the disease in:

- Ulcerative colitis (systemic therapy)
- Regional enteritis (systemic therapy)

8. *Respiratory Diseases*:

- Symptomatic sarcoidosis
- Berylliosis
- Aspiration pneumonitis
- Loeffler's syndrome not manageable by other means
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.

9. *Haematologic Disorders*:

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

10. *Neoplastic Diseases*: For palliative management of:

- Leukaemias and lymphomas in adults
- Acute leukaemia of childhood

11. 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.

12. Nervous System: Acute exacerbations of multiple sclerosis.

13. Miscellaneous:

- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
- Trichinosis with neurologic or myocardial involvement.
- As adjunctive therapy in the treatment of AIDS patients with moderate to

severe Pneumocystis carinii pneumonia (PCP) when given within the first 72 hours of initial anti-pneumocystis treatment.

CONTRAINDICATIONS

Methylprednisolone is contraindicated in patients with:

· Known hypersensitivity to methylprednisolone or any of the excipients used in the formulation

· Systemic fungal infections

PRECAUTIONS

METHYLPREDNISOLONE ALPHAPHARM IS NOT INDICATED FOR INTRATHECAL, EPIDURAL OR LOCAL INJECTION OR ANY OTHER UNSPECIFIED ROUTE OF ADMINISTRATION.

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

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise 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 along 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.

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

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

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

Administration of live, 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 methylprednisolone 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-tuberculous 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 chemophylaxis.

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

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.

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

Drug-induced secondary adrenocortical insufficiency may be minimised by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy, therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

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

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

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

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

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

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

observed.

Although controlled clinical trials have shown corticosteroid 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).

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.

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 blocking drugs (e.g. pancuronium). This acute myopathy is generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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

Use in Pregnancy (Category A)

Australian Categorisation Definition for Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Use in Lactation

Prednisolone is excreted in breast milk, therefore it is reasonable to assume that all corticosteroids are. No specific data is known for methylprednisolone sodium succinate.

Interactions with Other Medicines

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 inclined to occur.

Methylprednisolone has a wide spectrum of clinical use and is therefore used with numerous concurrent drugs. The interactions listed 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.

CLASS OF DRUG	DRUG(S) INVOLVED	DRUG(S) AFFECTED	MECHANISM	CLINICAL IMPLICATION
Antibiotic/ Antifungal therapy	Triacetyloleandomycin Erythromycin Ketoconazole Rifampicin	Methylprednisolone Methylprednisolone	Enzyme inhibition: Reduced methylprednisolone elimination Enzyme induction, increased clearance	Enhanced clinical effects and side effects of methylprednisolone May reduce efficacy; dosage adjustment may be required
Anticholinesterase	Neostigmine Pyridostigmine	Anticholinesterase		Precipitation of myasthenic crisis
Anticoagulants	Oral anticoagulants or heparin	Anticoagulant		Increased or decreased clotting. Monitor response. Adjust dose.
Anticonvulsants	e.g. Phenobarbitone, phenytoin	Methylprednisolone	Enzyme induction: increased clearance of methylprednisolone	May reduce methylprednisolone efficacy. Monitor clinical response. Adjust dose if necessary.
Antidiabetics	e.g. Insulin, glibenclamide, metformin	Antidiabetic	Diabetogenic effects of corticosteroid	May impair glucose control. Monitor glucose levels and adjust dose of antidiabetic therapy.
Antihypertensives	All antihypertensives	Antihypertensive	Mineralocorticoid effect of corticoid leading to raised blood pressure	May result in partial loss of hypertensive control.
Cardiac glycosides	Digoxin and related glycosides	Digoxin	Corticosteroid induced hypokalaemia (mineralocorticoid effect)	Potentiation of digoxin toxicity.
Diuretics	All potassium losing diuretics e.g. frusemide		Hypokalaemia	Enhanced toxicity. Monitor K^+ levels and supplement if required.
Immunising Agents	Live vaccine: poliomyelitis, BCG, mumps, measles, rubella, smallpox Killed Virulent Vaccines	Vaccine Vaccine	Corticosteroid induced immunosuppression Impaired immune response	May see increase toxicity from vaccine. Disseminated viral disease may occur. Reduced response to vaccine.

Immunosuppressants	Methotrexate Cyclosporin	Methylprednisolone Cyclosporin Methylprednisolone	Synergistic effect induced immunosuppression Mutual inhibition of metabolism.	May allow reduced dose of corticosteroid. Monitor cyclosporin A levels. Adjust dose as necessary.
Neuromuscular Blocking Agents	Pancuronium	Pancuronium		Partial reversal of neuromuscular block.
Psychotherapeutic	Anxiolytics Antipsychotics	CNS active drug	CNS effects of corticosteroid	Recurrence or poor control of CNS symptoms. May require dose adjustment.
Salicylates		Salicylate	Increased clearance and decreased plasma level	Apparent decrease in salicylate efficacy or salicylate toxicity on reduction of corticosteroid dose.
Sympathomimetic agents	e.g. Salbutamol		Increased response to sympathetic agents	Increased efficacy and potentially increased toxicity.

ADVERSE EFFECTS

Fluid and Electrolyte Disturbances	· Fluid retention · Potassium loss · Sodium retention · Hypokalaemic alkalosis · Congestive heart failure in susceptible patients · Hypertension
Musculoskeletal	· Muscle weakness · Steroid myopathy · Loss of muscle mass · Osteoporosis · Vertebral compression fractures · Pathologic fracture of long bones · Aseptic necrosis of femoral and humeral heads

	· Severe arthralgia · Tendon rupture, particularly of the Achilles tendon
Gastrointestinal	· Pancreatitis · Ulcerative oesophagitis · Abdominal distension · Peptic ulcer with possible perforation haemorrhage · Gastric haemorrhage · Perforation of the bowel Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.
Dermatological	· Impaired wound healing · Thin fragile skin · Petechiae and ecchymoses · Facial erythema · Increased sweating · May suppress reaction to skin tests
Neurological	· Convulsions · Headache · Vertigo · Increased intracranial pressure with papilloedema (pseudo-tumour cerebri) usually after treatment · Psychic derangements
Endocrine	· Menstrual irregularities · Suppression of growth in children · Development of Cushingoid state · Decreased carbohydrate tolerance · Manifestations of latent diabetes mellitus · Increased requirements for insulin or oral hypoglycaemic agents in

	diabetics · Secondary adrenocortical and pituitary unresponsiveness, (particularly in times of stress as in trauma, surgery or illness) · Suppression of pituitary (adrenal axis)
Ophthalmic	· Posterior subcapsular cataracts · Glaucoma · Increased intraocular pressure · Exophthalmos
Metabolic	Negative nitrogen balance due to protein catabolism The following adverse events are related to parenteral corticosteroid therapy: · Hyperpigmentation or hypopigmentation · Subcutaneous and cutaneous atrophy · Sterile abcess · Urticaria · Nausea and vomiting
Immune System	· Masking of infections · Latent infections becoming active · Opportunistic infections · Hypersensitivity reactions including anaphylaxis with or without circulatory collapse, cardiac arrest, bronchospasm, or hypertension
Cardiovascular	· Myocardial rupture following a myocardial infarction · Hypotension · Cardiac arrthymias
Other	Persistent hiccups with high doses of corticosteroids.

DOSAGE AND ADMINISTRATION

Methylprednisolone Alphapharm may be administered by intravenous or deep intramuscular injection or by intravenous infusion. The preferred method for initial emergency use is intravenous injection. Prepare solution as directed for intravenous (or intramuscular) administration (see Reconstitution). The desired dose, if 250 mg or less, may be administered intravenously over at least 5 minutes. Intramuscular injections (250 mg or less) should be injected slowly into a large muscle.

When high dose therapy is indicated (i.e. greater than 250 mg), the recommended dose of Methylprednisolone Alphapharm is 30 mg/kg administered over at least 30 minutes (see PRECAUTIONS, ADVERSE EFFECTS and OVERDOSAGE). This dose may be repeated every 4 to 6 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.

In other indications, initial dosage will vary from 10 to 500 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, up to 250 mg, should be given intravenously over a period of at least 5 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 per kg every 24 hours.

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

Pneumocystis carinii pneumonia

For patients diagnosed with *Pneumocystis carinii* pneumonia (PCP), presenting with a $Pa0_2$ (arterial oxygen pressure) under 55 mm Hg on room air, or where respiratory failure is considered likely, the following regimen should be administered:

Administer 40 mg of Methylprednisolone Alphapharm Powder for Solution for Injection intravenously every six hours for 5 to 7 days. Upon improvement, oral prednisolone should be instituted with the following tapering regimen:

60 mg (divided four times daily) for 2 days

50 mg (divided twice daily) for 2 days

40 mg (divided twice daily) for 2 days

30 mg (divided twice daily) for 2 days

20 mg (divided twice daily) for 2 days

15 mg (divided twice daily) for 2 days

10 mg (divided twice daily) for 2 days

5 mg (divided twice daily) for 2 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.

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

Summary of dosage and administration recommendations for

Intravenous use

DOSE	ADMINISTRATION TIME
Greater than 2 g	At least 30 minutes
1 g	At least 30 minutes
500 mg	At least 30 minutes
250 mg	At least 5 minutes
125 mg	At least 5 minutes
Less than 40 mg	At least 5 minutes

Intramuscular use

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

Reconstitution

Methylprednisolone Alphapharm should be reconstituted with 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 Methylprednisolone Alphapharm be used immediately upon preparation.

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

PRODUCT STRENGTH	DILUENT VOLUME RECOMMENDED	RESULTING CONCENTRATION
40 mg	2 mL	20 mg/mL
500 mg	4 or 8 mL	125 or 62.5 mg/mL
1 g	8 or 16 mL	125 or 62.5 mg/mL

Preparation of Solutions for Intravenous Infusion

To prepare an intravenous solution, first reconstitute powder for injection as directed in the reconstitution section. The reconstituted solution may then be added to Glucose Intravenous Infusion 5%, Sodium Chloride Intravenous Infusion 0.9% or Sodium Chloride 0.9% and Glucose 5% Intravenous Infusion; the resulting admixtures should be used immediately and is for SINGLE USE ONLY.

Compatibility and Stability

It is recommended to administer Methylprednisolone Alphapharm separately from other drugs and as either IV injection, through an IV medication chamber, microburette, or as an IV "piggy-back" solution, whenever possible, to avoid compatibility and stability problems. The IV 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 solubilising ability of methylprednisolone.

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 Methylprednisolone Alphapharm Powder for Injection. Acute overdose may possibly aggravate pre-existing disease states such as ulceration of the gastrointestinal tract, electrolyte disturbances, infections, diabetes and oedema.

High doses of methylprednisolone, when given repeatedly, 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 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.

Contact the Poisons Information Centre on 131126 (Australia) for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Methylprednisolone Alphapharm 40 mg and 500 mg, powder for injection are a sterile white powder, available in packs of 1 vial* and 5 vials.

Methylprednisolone Alphapharm 1 g, powder for injection is a sterile white powder, available in packs of 1 vial and 5 vials.

*Currently not marketed in Australia.

Storage

Store below 25°C. Protect from light.

When reconstituted using Sterile Water for Injections, the resulting solution should be used immediately. Discard any unused portion.

Product is for single use in one patient only. Discard any residue.

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited

(ABN 93 002 359 739)

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 8 August 2011.