

## **MEDROL®**

### **Methylprednisolone**

#### **4 mg or 100 mg tablets**

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## **PRESENTATION**

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MEDROL tablets 4 mg (methylprednisolone) are white, flat, elliptical, coded "MEDROL 4" on one side, double scored on the reverse.

MEDROL tablets 100 mg are light blue, round, biconvex cross-scored, coded "Upjohn 3379".

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## **USES**

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### **Mechanism of Action**

Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone, even less tendency than prednisolone to induce sodium and water retention. The relative potency of methylprednisolone to hydrocortisone is at least four to one.

### **Pharmacokinetics**

#### ***Absorption***

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

The absolute bioavailability of methylprednisolone in normal healthy subjects is generally high (82% to 89%) following oral administration. Methylprednisolone is rapidly absorbed and the maximum plasma methylprednisolone concentration is achieved around 1.5 to 2.3 hours across doses following oral administration in normal healthy adults.

The mean oral time of peak concentration is 1.1 - 2.2 hours.

#### ***Distribution***

Methylprednisolone is widely distributed throughout the body and is described by a two-compartment model. The mean volume of distribution reported in 34 adult volunteers ranged from 41 to 61.5 L.

Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.

Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier the placental barrier, and is secreted in breast milk. The plasma protein binding of methylprednisolone in humans is approximately 77%.

MEDROL readily crosses the blood-brain barrier into the central nervous system with peak CSF levels being 5 - 6% of the corresponding plasma levels. Methylprednisolone peak CSF levels occurred within five minutes to one hour after IV administration of a 500mg dose to patients with lupus cerebritis.

### ***Biotransformation or Metabolism***

In humans, methylprednisolone is metabolised in the liver to inactive metabolites, the major ones 20 $\alpha$ -hydroxymethylprednisolone and 20 $\beta$ -hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4 enzyme. (For a list of drug interactions based on CYP3A4-mediated metabolism, see **Interactions** section).

### ***Elimination***

The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours

Following IV administration of radiolabelled 6-methylprednisolone to six cancer patients, 75% of total reactivity was recovered in the urine after 96 hours and 9% in the faeces after five days. Twenty percent of the total dose was excreted in the bile, but the time course was not cited.

### ***Use in the Renal Disease***

No dosing adjustments are necessary in renal failure. Methylprednisolone is haemodialysable (see **Warnings and Precautions, Renal and Urinary**).

## **Indications**

MEDROL (methylprednisolone) is indicated in the following conditions:

### ***Endocrine Disorders***

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).

#### ***Congenital adrenal hyperplasia***

- Nonsuppurative thyroiditis
- Hypercalcemia associated with cancer

### ***Non-Endocrine Disorders***

#### ***Rheumatic Disorders***

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

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

#### *Collagen Diseases*

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

- systemic lupus erythematosus
- systemic dermatomyositis (polymyositis)
- polymyalgia rheumatic
- giant cell arteritis
- acute rheumatic carditis

#### *Dermatologic Diseases*

- pemphigus
- bullous dermatitis herpetiformis
- severe erythema multiforme (Stevens-Johnson syndrome)
- exfoliative dermatitis
- mycosis fungoides
- severe psoriasis
- severe seborrheic dermatitis

### *Allergic States*

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

- seasonal or perennial allergic rhinitis
- serum sickness
- bronchial asthma
- drug hypersensitivity reactions
- contact dermatitis
- atopic dermatitis

### *Ophthalmic Diseases*

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

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

### *Respiratory Diseases:*

- symptomatic sarcoidosis
- Loeffler's syndrome not manageable by other means
- Berylliosis

- fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
- aspiration pneumonitis

#### *Haematologic Disorders*

- idiopathic thrombocytopenia purpura in adults
- secondary thrombocytopenia in adults
- acquired (autoimmune) haemolytic anaemia
- erythroblastopenia (RBC anaemia)
- congenital (erythroid) hypoplastic anaemia

#### *Neoplastic Diseases*

For palliative management of:

- leukemias and lymphomas in adults
- acute leukaemia of childhood

#### *Edematous States*

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

#### *Gastrointestinal Diseases*

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

- ulcerative colitis
- regional enteritis

#### *Nervous system*

- Acute exacerbations of multiple sclerosis
- Management of oedema associated with brain tumour.

#### *Miscellaneous*

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

#### *Organ Transplantations*

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## DOSAGE AND ADMINISTRATION

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

The lowest possible dose of corticosteroid should be used to control the condition under treatment and when reduction in dosage is possible, the reduction should be gradual.

The initial dosage of MEDROL Tablets may vary from 4 mg to 48 mg of methylprednisolone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required.

Do not halve the tablets.

Clinical situations in which high dose therapy may be indicated include multiple sclerosis (200 mg/day), cerebral oedema (200 - 1,000 mg/day), and organ transplantation (up to 7 mg/kg/day). The initial dosage should be maintained or adjusted until a satisfactory response is noted. If, after a reasonable period of time, there is a lack of satisfactory clinical response,

MEDROL should be discontinued and the patient transferred to other appropriate therapy. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

It should be emphasised that dosage requirements are variable and must be individualised on the basis of the disease under treatment and the response of the patient. After a favourable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of MEDROL for a period of time consistent with the patient's condition.

### ***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 one month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

### ***ADT Alternate Day Therapy***

Alternate day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticosteroid is administered every other morning. The purpose of this mode of therapy is to provide a patient requiring long-term pharmacologic dose treatment with the beneficial

effects of corticoids while minimising certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms and growth suppression in children.

The rationale for this treatment schedule is based on two major premises:

The anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects, and

Administration of the corticosteroid every other morning allows for re-establishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-corticosteroid day.

The following should be kept in mind when considering alternate day therapy:

Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of corticosteroids.

ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticosteroid therapy is anticipated.

In less severe disease processes in which corticosteroid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible, particularly when subsequent use of alternate day therapy is intended.

Once control has been established, two courses are available:

- Change to ADT and then gradually reduce the amount of corticosteroid given every other day, or
- Following control of the disease process reduce the daily dose of corticosteroid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (i) may be preferable.

Because of the advantages of ADT, it may be desirable to try patients on this form of therapy who have been on daily corticosteroids for long periods of time (eg. patients with rheumatoid arthritis). Since these patients may already have suppressed HPA axis, establishing them on ADT may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.

As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (e.g. dexamethasone and betamethasone).

The maximal activity of the adrenal cortex is between 2.00am and 8.00am, and it is minimal between 4.00pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).

In using ADT it is important, as in all therapeutic situations, to individualise and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-corticosteroid day. Other symptomatic therapy may be added or increased at this time if needed.

In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticosteroid dose for control. Once control is again established alternate day therapy may be reinstated.

Although many of the undesirable features of corticosteroid therapy can be minimised by ADT, as in any therapeutic situation, the physician must carefully weigh the benefit risk ratio for each patient in whom corticosteroid therapy is being considered.

#### *Use in Renal Disease*

No dosing adjustments are necessary in renal failure. Methylprednisolone is haemodialysable.

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## CONTRAINDICATIONS

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MEDROL is contraindicated

- in patients who have systemic infections unless specific anti-infective therapy is given
- in patients with known hypersensitivity to methylprednisolone or any component of the formulation.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see **Warnings and Precautions**).

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## WARNINGS AND PRECAUTIONS

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### *Immunosuppressive Effects/Increased Susceptibility to Infections*

Due to their suppression of the inflammatory response and immune function, corticosteroids may increase susceptibility to fungal, bacterial and viral infections and their severity. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, they should seek urgent medical attention. Passive immunisation is recommended if non-immune patients who come into contact with chicken

pox. If a diagnosis of chicken pox is confirmed the illness warrants specialist care and urgent treatment.

The immunosuppressive effects of corticosteroids may also result in activation of latent infection or exacerbation of existing infection. Corticosteroids should be used with great care in patients with known or suspected parasitic infections such as *Strongyloides* infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicaemia.

It is important to note that corticosteroids may also mask some signs of infection which may reach an advanced stage before the infection is recognised.

There may also be decreased resistance and inability to localize infection when corticosteroids are used.

Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal.

With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. MEDROL is not recommended for use in patients with septic shock or sepsis syndrome. The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, a systematic review concluded that short-course, high-dose corticosteroids did not support their use. However, meta-analyses and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in those with vasopressor-dependent septic shock.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids and should be postponed until at least three months after stopping corticosteroid therapy. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

The use of MEDROL (methylprednisolone) tablets 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.

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

### ***Blood and Lymphatic System***

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

### ***Hypersensitivity reactions***

Allergic reactions (e.g. angioedema) may occur.

Because rare instances of 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.

### ***Endocrine***

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 the use of alternate-day therapy (see **Dosage and Administration, Alternate Day 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.

Drug-induced adrenocortical insufficiency may be minimised by gradual reduction of dosage, however symptoms may persist for months after discontinuation of therapy.

It is important to note that acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Therefore, withdrawal of corticosteroids should always be gradual.

In patients on corticosteroid therapy (or those who have discontinued treatment but continue to experience symptoms of adrenal insufficiency) who are subjected to unusual stress such as intercurrent illness, trauma or surgery, increased dosage (or reinstatement) of rapidly acting corticosteroids may be required. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

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

Corticosteroids should be used with caution in patients with hypothyroidism as there is potential for an enhanced effect of corticosteroids in these patients.

### ***Metabolism and Nutrition***

Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes and predisposes those on long term corticosteroid therapy to diabetes

mellitus; therefore, corticosteroids should be used with caution in patients with, or a family history of, diabetes mellitus.

### ***Psychiatric***

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

Symptoms of potentially severe psychiatric adverse reactions associated with corticosteroid use typically emerge within a few days or weeks of starting treatment.

Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

Psychological effects have also 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.

### ***Nervous System***

Corticosteroids should be used with caution in patients with seizure disorders.

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

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

### ***Ocular***

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible risk of corneal scarring, loss of vision and 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.

Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

### ***Cardiovascular***

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

Corticosteroids should be used with caution in patients with hypertension.

### ***Gastrointestinal***

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain.

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

### ***Hepatobiliary***

Corticosteroids should be used with caution in patients with hepatic failure.

There is an enhanced effect of corticosteroids on patients with cirrhosis.

### ***Musculoskeletal***

Corticosteroids should be used with caution in patients with myasthenia gravis who are receiving anticholinesterase therapy as corticosteroid use may decrease plasma anticholinesterase activity. An acute myopathy has been reported 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 anticholinergics, such as neuromuscular blocking drugs (e.g, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. 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 patients with osteoporosis. Osteoporosis is also a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

Corticosteroid should be used with caution in patients with Duchenne's muscular dystrophy since transient rhabdomyolysis and myoglobinuria have been reported following strenuous activities.

Corticosteroids should also be used with caution in patients with previous steroid myopathy.

### ***Renal and Urinary***

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

### ***Investigations***

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

### ***Discontinuation***

A steroid “withdrawal syndrome”, seemingly unrelated to adrenocortical insufficiency, may occur following abrupt discontinuance of glucocorticoids. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels (see **Adverse Events, General disorders and administration site conditions**)

### ***Injury, Poisoning and Procedural Complications***

High doses of systemic corticosteroids should not be used for the treatment of traumatic brain injury.

### ***Carcinogenesis, mutagenesis, impairment of fertility***

There is no evidence that corticosteroids are carcinogenic, mutagenic, or impair fertility.

### ***Use in pregnancy and Lactation***

#### ***Pregnancy***

The benefits of the use of Medrol in pregnant women and those of childbearing potential should be carefully weighed against any potential risk to the mother and embryo of foetus. Since there is inadequate evidence of safety in human pregnancy, Medrol should be used in pregnancy only if clearly needed.

Some animal studies have shown that corticosteroids may cause foetal malformations (cleft palate, skeletal malformations) and abortion. Reduced placental and birth weight have also been recorded after long-term maternal treatment along with potential for suppression of the adrenal cortex in newborns.

Corticosteroids readily cross the placenta. One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids. Although neonatal adrenal insufficiency appears to be rare in infants who were exposed *in utero* to corticosteroids, those exposed to substantial doses of corticosteroids must be carefully observed and evaluated for signs of adrenal insufficiency.

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

#### ***Lactation***

Corticoids are excreted in breast milk. Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants.

Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risks to the infant.

### ***Use in Children***

Corticosteroids may cause growth retardation in infancy, childhood and adolescence. The effects may be irreversible; therefore long-term daily-divided doses of corticosteroids should be avoided in these patients.

In infants, children and adolescents, corticosteroid treatment should be administered where possible as a single dose on alternate days for the shortest possible duration.

If prolonged therapy is necessary, growth and development of these patients should be carefully monitored.

Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of methylprednisolone.

### ***Use in Elderly***

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

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## **ADVERSE EFFECTS**

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The adverse effects listed in the table below are typical for all systemic corticosteroids. Their inclusion in this list does not necessarily indicate that the specific event has been observed with Medrol.

<i>Vascular disorders</i>	Hypertension Hypotension
<i>Cardiac disorders</i>	Heart failure congestive (in susceptible patients)
<i>Respiratory, thoracic and mediastinal disorders</i>	Hiccups
<i>Musculoskeletal and connective tissue disorders</i>	Arthralgia Growth retardation Muscle atrophy Muscular weakness Myalgia Steroid myopathy Neuropathic arthropathy

	Avascular osteonecrosis, Osteoporosis, Pathologic fractures
<i>Gastrointestinal disorders</i>	Abdominal distension Abdominal pain Diarrhoea Dyspepsia Intestinal perforation Nausea Oesophagitis Oesophagitis ulcerative Peptic ulcer with possible perforation, Peptic ulcer haemorrhage Pancreatitis Gastric haemorrhage Oesophageal candidiasis
<i>Investigations</i>	Alanine transaminase increased Aspartate transaminase increased Blood alkaline phosphatase increased Blood potassium decreased Carbohydrate tolerance decreased Intraocular pressure increased Increased calcium excretion / Urine calcium increased
<i>Skin and subcutaneous tissue disorders</i>	Angioedema Ecchymosis Erythema Hirsutism Hyperhidrosis Petechiae Pruritus Rash Skin atrophy Skin striae Urticaria Acne Telangiectasia Thin fragile skin Impaired wound healing
<i>Psychiatric disorders</i>	Abnormal behaviour Affective disorder (including affect lability, depressed mood, euphoric mood, psychological dependence, suicidal ideation) Behavioural disturbances (including

	<p>anxiety, confusional state, insomnia, irritability)</p> <p>Mental disorder</p> <p>Mood swings</p> <p>Personality change</p> <p>Psychotic behaviour</p> <p>Psychotic disorders (including mania, delusion, hallucination and schizophrenia [aggravation of])</p>
<i>Nervous system disorders</i>	<p>Amnesia</p> <p>Cognitive disorder</p> <p>Convulsions</p> <p>Dizziness</p> <p>Headache</p> <p>Intracranial pressure increased (with papilloedema [benign intracranial hypertension])</p>
<i>Endocrine disorders</i>	<p>Cushingoid symptoms,</p> <p>Hypopituitarism</p> <p>Manifestation of latent diabetes,</p> <p>Suppression of growth in infants, children and adolescents.</p>
<i>Reproductive system and breast disorders</i>	<p>Menstruation irregularities and amenorrhoea</p>
<i>Metabolism and nutrition disorders</i>	<p>Alkalosis hypokalaemic</p> <p>Fluid retention</p> <p>Increased appetite (which may result in weight gain)</p> <p>Increased requirements for insulin or oral hypoglycaemic agents in diabetics</p> <p>Metabolic acidosis</p> <p>Sodium retention</p> <p>Negative nitrogen and calcium balance</p>
<i>Eye disorders</i>	<p>Cataract subcapsula,</p> <p>Glaucoma</p> <p>Exophthalmos</p> <p>Intraocular pressure increased</p> <p>Corneal or scleral thinning</p> <p>Exacerbation of ophthalmic viral or fungal disease</p>
<i>Ear and labyrinth disorders</i>	<p>Vertigo</p>
<i>Infections and Infestations</i>	<p>Increased susceptibility to and severity of infections with suppression of clinical symptoms and signs</p>

	<p>Opportunistic infections  Recurrence of dormant tuberculosis.</p>
<i>Immune system disorders</i>	<p>Drug hypersensitivity (including anaphylactic reaction and anaphylactoid reaction,  Suppression of reactions to skin tests</p>
<i>General disorders and administration site conditions</i>	<p>Fatigue  Impaired healing  Malaise  Leucocytosis</p> <p>Steroid “withdrawal syndrome,” 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.</p>
<i>Injury, poisoning and procedural complications</i>	<p>Long bone and spinal compression fracture  Tendon rupture (particularly of the Achilles tendon)</p>

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## INTERACTIONS

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Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is metabolized mainly by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6 $\beta$ -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 concentration of methylprednisolone. These include:

- Antifungals such as ketoconazole and itraconazole
- Antiemetics, such as aprepitant and fosaprepitant
- Immunosuppressants such as cyclosporine
- Macrolide antibacterials such as clarithromycin, erythromycin and troleanomycin

- HIV-Protease inhibitors
- Ciclosporin
- Ritonavir
- Diltiazem
- Grapefruit juice

Coadministration of CYP3A4 inhibitors may require titration of methylprednisolone 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 methylprednisolone. These include:

- Phenobarbital
- Phenytoin
- Rifampicin
- Rifabutin
- Carbamazepine
- Primidone
- Aminogluethimide

Coadministration of these substances may require an increase in methylprednisolone dosage to achieve the desired result.

### ***CYP3A4 SUBSTRATES***

In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be inhibited or induced, 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.

### ***OTHER INTERACTIONS***

***Other interactions and effects that occur with methylprednisolone are described below.***  
***Antacids***

Concurrent use may decrease absorption of corticosteroids. Efficacy may be reduced sufficiently to require dosage adjustments in patients receiving small doses of corticosteroids.

### ***Antidiabetic agents***

Corticosteroids may increase blood glucose levels. Dose adjustments of antidiabetic therapy may be required with concurrent therapy.

### ***Oral anticoagulants***

The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices (such as INR or prothrombin time) should be monitored to maintain the desired anticoagulant effects.

### ***Anticholinergics***

Corticosteroids may influence the effect of anticholinergics.

Acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs.

Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.

### ***Cardiac glycosides***

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

### ***Oral contraceptives***

Oral contraceptives retard the metabolism of corticosteroids due to increased binding to globulin, resulting in increased plasma levels of corticosteroids and potentiating their biological effect. The dose of corticosteroids may need to be adjusted when commencing or stopping oral contraceptive therapy.

### ***Diuretics***

Excessive potassium loss may be experienced with concurrent use of corticosteroids and potassium depleting diuretics (such as frusemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide).

### ***Mifepristone***

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

### ***NSAIDs***

Concomitant administration may increase the risk of gastrointestinal bleeding and ulceration.

Methylprednisolone may increase the renal clearance of aspirin. This resulting decrease in salicylate serum levels could lead to an increased risk of salicylate toxicity when methylprednisolone is withdrawn.

### ***Somatropic***

Concomitant administration may inhibit the growth promoting effect of somatropin.

### ***Sympathomimetics***

There is an increased risk of hypokalaemia with concurrent high doses of corticosteroids and sympathomimetics such as salbutamol, salmeterol, terbutaline or formoterol.

### ***Antivirals***

Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.

Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.

### ***Antifungals***

The risk of hypokalaemia may be increased with amphotericin.

### ***Vaccines***

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

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## **OVERDOSAGE**

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

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## **PHARMACEUTICAL PRECAUTIONS**

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### ***Instructions for Use/Handling***

Do not halve tablets

### ***Shelf life***

Medrol 4 mg tablets: 18 months at Store at or below 25°C.

Medrol 100 mg tablets: 60 months at stored at or below 25°C

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## MEDICINE CLASSIFICATION

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Prescription Medicine.

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## PACKAGE QUANTITIES

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MEDROL tablets 4mg are available in bottles of 100. The blister packs of 100 tablets are registered but not distributed in New Zealand.

MEDROL tablets 100mg are available in bottles of 20.

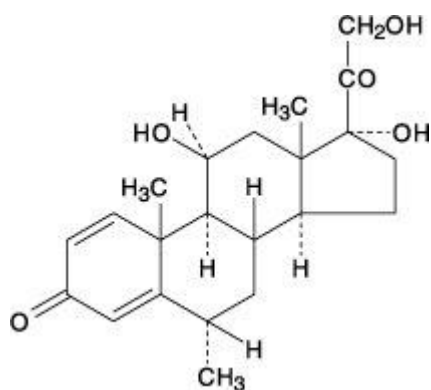
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## FURTHER INFORMATION

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The chemical name for methylprednisolone is pregna-1, 4-diene-3, 20-dione,11,17,21-trihydroxy-6-methyl-(6 $\alpha$ , 11 $\beta$ ).

The structural formula is represented below



The CAS Number is 83-43-2. The molecular weight is 374.48 and the empirical formula is C<sub>22</sub>H<sub>30</sub>O<sub>5</sub>.

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## NAME AND ADDRESS

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## **DATE OF PREPARATION**

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09 January 2012