AUSTRALIAN PRODUCT INFORMATION – DEPO-MEDROL® (METHYLPREDNISOLONE ACETATE) SUSPENSION FOR INJECTION

For Intramuscular, Intra-articular, Soft Tissue or Intralesional Injection Only

Not for Intravenous, Intrathecal or Epidural Use

1. NAME OF THE MEDICINE

Methylprednisolone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of DEPO-MEDROL contains 40 mg of methylprednisolone acetate as the active substance.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Suspension for Injection

White to off white suspension when mixed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

A. For Intramuscular Administration

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, the intramuscular use of DEPO-MEDROL is indicated as follows:

1. Endocrine Disorders

- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone acetate 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 acetate 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

- Congenital adrenal hyperplasia
- Hypercalcaemia associated with cancer
- Non-suppurative thyroiditis.

2. Rheumatic Disorders

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

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

3. Collagen Diseases

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

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

4. Dermatological Diseases

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

- Mycosis fungoides.

5. Allergic States

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

- Bronchial asthma
- Drug hypersensitivity reactions
- Contact dermatitis
- Urticarial transfusion reactions
- Atopic dermatitis
- Acute non-infectious laryngeal oedema (adrenaline is the drug of first choice)
- Serum sickness.

6. Ophthalmic Diseases

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

- Herpes zoster ophthalmicus
- Sympathetic ophthalmia
- Iritis, iridocyclitis
- Anterior segment inflammation
- Chorioretinitis
- Allergic conjunctivitis
- Diffuse posterior uveitis
- Allergic corneal marginal ulcers
- Optic neuritis
- Keratitis.

7. Gastrointestinal Diseases

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

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

8. Respiratory Diseases

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

9. Haematological Disorders

- Acquired (autoimmune) haemolytic anaemia
- Erythroblastopenia (RBC anaemia)
- Secondary thrombocytopenia in adults
- Congenital (erythroid) hypoplastic anaemia.

10. Neoplastic Diseases

For palliative management of:

- Leukaemias and lymphomas in adults
- Acute leukaemia in 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. Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate anti-tuberculous chemotherapy
- Trichinosis with neurological or myocardial involvement.

B. For Intra-Articular or Soft Tissue Administration

DEPO-MEDROL is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- Synovitis of osteoarthritis
- Epicondylitis
- Rheumatoid arthritis
- Acute non-specific tenosynovitis

- Acute and subacute bursitis
- Post-traumatic osteoarthritis
- Acute gouty arthritis.

C. For Intralesional Administration

DEPO-MEDROL is indicated for intralesional use in the following conditions:

- Keloids
- Discoid lupus erythematosus
- Necrobiosis lipoidica diabeticorum
- Alopecia areata
- Localised hypertrophic, infiltrated inflammatory lesions of Lichen Planus, psoriatic plaques, Granuloma Annulare and Lichen Simplex Chronicus (neurodermatitis).

DEPO-MEDROL may also be useful in cystic tumours of an aponeurosis or tendon (ganglia).

4.2 Dose and method of administration

Dosage

Because of possible physical incompatibilities, DEPO-MEDROL should not be diluted or mixed with other solutions.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Each vial of DEPO-MEDROL is for single use in a single patient only. Discard any unused product.

It is critical that, during administration of DEPO-MEDROL, appropriate technique be used and care taken to assure proper placement of drug.

A. Administration for Local Effect

Therapy with DEPO-MEDROL does not obviate the need for the conventional measures usually employed. Although this method of treatment will ameliorate symptoms, it is in no sense a cure, and the hormone has no effect on the cause of the inflammation.

1. Rheumatoid and Osteoarthritis

The dose for intra-articular administration depends upon the size of the joint and varies with the severity of the condition in the individual patient. In chronic cases, injections may be repeated at intervals ranging from one to five or more weeks depending upon the degree of relief obtained from the initial injection. The doses in the following table are given as a general guide.

Size of Joint	Examples	Range of Dosage
Large	Knees Ankles Shoulders	20 to 80 mg
Medium	Elbows Wrists	10 to 40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4 to 10 mg

Procedure: It is recommended that the anatomy of the joint involved be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20 to 24-gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Procaine infiltration is elective. The aspiration of only a few drops of joint fluid proves the needle has entered the joint space. **The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves.** With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the desired amount of DEPO-MEDROL. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of the synovial fluid and the suspension. The site is covered with a small sterile dressing. Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal and hip joints. Since difficulty is not infrequently encountered in entering the hip joint, precautions should be taken to avoid any large blood vessels in the area. Joints not suitable for injection are those that are anatomically inaccessible such as the spinal joints and those like the sacroiliac joints that are devoid of synovial space. Treatment failures are most frequently the result of failure to enter the joint space. Little or no benefit follows injection into surrounding tissue. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile. Local therapy does not alter the underlying disease process and whenever possible, comprehensive therapy including physiotherapy and orthopaedic correction should be employed.

Following intra-articular steroid therapy, care should be taken to avoid overuse in joints in which symptomatic benefit has been obtained. Negligence in this matter may permit an increase in joint deterioration that will more than offset the beneficial effects of the steroid. Unstable joints should not be injected. Repeated intra-articular injection may in some cases result in instability of the joint. X-ray follow-up is suggested in selected cases to detect deterioration.

If a local anaesthetic is used prior to injection of DEPO-MEDROL, the anaesthetic package insert should be read carefully and all the precautions observed.

2. Bursitis

The area around the injection site is prepared in a sterile way, and a wheal at the site made with 1% procaine hydrochloride solution. A 20 to 24-gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place, and the aspirating syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

3. Miscellaneous: Ganglion, Tendinitis, Epicondylitis

In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken, following application of a suitable antiseptic to the overlying skin, to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when placed on a stretch. When treating conditions such as epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into the area. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst. In many cases, a single injection causes a marked decrease in the size of the cystic tumour and may affect disappearance.

NOTE: Due to the absence of a true tendon sheath, the Achilles tendon should not be injected with DEPO-MEDROL.

The dose in the treatment of the various conditions of the tendinous or bursal structures listed above varies with the condition being treated and ranges from 4 mg to 30 mg. In recurrent or chronic conditions, repeated injections may be necessary.

The usual sterile precautions should be observed with each injection.

4. Injections for Local Effect in Dermatological Conditions

Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 mg to 60 mg is injected into the lesion. It may be necessary to distribute doses ranging from 20 mg to 40 mg by repeated local injections in the case of large lesions. Care should be taken to avoid injection of sufficient material to cause blanching, since this may be followed by a small slough. One to four injections are usually employed, the intervals between injections varying with the type of lesion being treated and the duration of improvement produced by the initial injection.

B. Administration for Systemic Effect

The intramuscular dosage will vary with the condition being treated. When a prolonged effect is desired, the weekly dose may be calculated by multiplying the daily oral dose by 7 and given as a single intramuscular injection.

Dosage must be individualised according to the severity of the disease and response of the patient. For infants and children, the recommended dosage will have to be reduced, but dosage should be governed by the severity of the condition rather than by strict adherence to the ratio indicated by age or body weight.

Hormone therapy is an adjunct to, and not a replacement for, conventional therapy. Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. The severity, prognosis and expected duration of the disease and the reaction of the patient to medication are primary factors in determining dosage. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper gastrointestinal X-rays are desirable in patients with an ulcer history or significant dyspepsia.

In patients with **adrenogenital syndrome**, a single intramuscular injection of 40 mg every two weeks may be adequate.

For maintenance of patients with **rheumatoid arthritis**, the weekly intramuscular dose will vary from 40 mg to 120 mg.

The usual dosage for patients with **skin lesions** benefited by systemic corticoid therapy is 40 mg to 120 mg of methylprednisolone acetate administered intramuscularly at weekly intervals for one to four weeks. In chronic contact dermatitis repeated injections at 5 to 10 day intervals may be necessary. In seborrhoeic dermatitis, a weekly dose of 80 mg may be adequate to control the condition.

Following intramuscular administration of 80 mg to 120 mg to **asthmatic patients**, relief may result within 6 to 48 hours and persist for several days to two weeks.

If signs of stress are associated with the condition being treated, the dosage of the suspension should be increased. If a rapid hormonal effect of maximum intensity is required, the intravenous administration of highly soluble methylprednisolone sodium succinate (SOLU-MEDROL®) is indicated.

4.3 Contraindications

- Systemic fungal infections
- Known hypersensitivity to methylprednisolone or any component of the formulation
- Intravenous, intrathecal, extradural, epidural or any unspecified route of administration
- Administration of live or live, attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids (see Section 4.4 Special warnings and precautions for use - Immunosuppressant Effects/Increased Susceptibility to Infections).

4.4 Special warnings and precautions for use

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

Administration Precautions

This product is not suitable for multidose use. Following administration of the desired dose, any remaining suspension should be discarded.

While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physicochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring dermal and/or subdermal changes may form depressions in the skin at the injection site. The degree to which this reaction occurs will vary with the amount of adrenal steroid injected. Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed.

In order to minimise the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into the area of the lesion should be made whenever possible. The technique of intra-articular and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

Methylprednisolone acetate should not be administered by any route other than those listed under Section 4.1 Therapeutic indications. It is critical that, during administration of methylprednisolone acetate, appropriate technique be used and care taken to assure proper placement of drug.

Severe medical events have been reported in association with the contraindicated intrathecal/epidural routes of administration (see Section 4.8 Adverse effects (undesirable effects)). Appropriate measures must be taken to avoid intravascular injection.

Immunosuppressant Effects/Increased Susceptibility to Infections

Corticosteroids increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, 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.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

Do not use intra-articularly, intrabursally or for intratendinous administration for local effect in the presence of acute infection.

A clinical trial in patients with septic shock failed to establish the efficacy of DEPO-MEDROL for these conditions. Thus, routine use in septic shock is not recommended. The study also suggests that treatment of these conditions with DEPO-MEDROL may increase the risk of mortality in certain patients (i.e., patients with elevated serum creatinine levels or patients who develop secondary infections after DEPO-MEDROL).

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 DEPO-MEDROL in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate anti-tuberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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

Immune System Effects

Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/anaphylactoid 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.

Allergic skin reactions have been reported apparently related to the excipients in the formulation. Rarely has skin testing demonstrated a reaction to methylprednisolone acetate *per se*.

Cardiac Effects

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidaemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects if high doses and/or prolonged courses are used. When using corticosteroids in these patients, attention should be paid to risk modification and additional cardiac monitoring should be considered.

Use of systemic corticosteroid is not recommended in patients with congestive heart failure.

Vascular Effects

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

Corticosteroids should be used with caution in patients with hypertension.

Endocrine Effects

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

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

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

Drug-induced secondary adrenocortical insufficiency may be minimised by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

A steroid "withdrawal syndrome", seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, joint pain,

desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

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

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

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

Hepatobiliary Effects

Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore, appropriate monitoring is required.

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

Ocular Effects

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

Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos or increased intraocular pressure which may result in glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses.

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

If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes.

Psychiatric Effects

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

Potentially severe psychiatric adverse reactions may occur with systemic steroids (see Section 4.8 Adverse effects (undesirable effects)). Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Gastrointestinal Effects

High doses of corticosteroids may produce acute pancreatitis.

Corticosteroid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

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

Nervous System Effects

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

Corticosteroids should be used with caution in patients with myasthenia gravis (see Section 4.4 Special warnings and precautions for use - Musculoskeletal Effects).

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

Musculoskeletal Effects

An acute myopathy has been described with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis) or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Cases of rhabdomyolysis have been reported. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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

Metabolism and Nutrition

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

Investigations

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

Injury, Poisoning and Procedural Complications

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

Other

Aspirin and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see Section 4.5 Interactions with other medicines and other forms of interactions - CYP3A4 Substrates, *NSAIDs*).

In post-marketing experience tumour lysis syndrome (TLS) has been reported in patients with malignancies, including haematological malignancies and solid tumours, following the use of systemic corticosteroids alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumours that have a high proliferative rate, high tumour burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

Additional Precautions Specific for Parenteral Corticosteroids

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motions, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided.

Corticosteroids should not be injected into unstable joints.

Sterile technique is necessary to prevent infections or contamination.

The slower rate of absorption by intramuscular administration should be recognised.

Use in Renal Impairment

Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone. Corticosteroids should be used with caution in patients with renal insufficiency.

Use in the Elderly

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

Paediatric Use

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily,

divided-dose glucocorticoid therapy and use of such a regimen should be restricted to the most urgent indications.

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

High doses of corticosteroids may produce pancreatitis in children.

Effects on Laboratory Tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Methylprednisolone has a wide spectrum of clinical use and is therefore used with numerous concurrent drugs. The interactions summarised in the following table 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.

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolised by the CYP3A4 enzyme. CYP3A4 catalyses 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 Inhibitors

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

CYP3A4 Inducers

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

CYP3A4 Substrates

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

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

Table 1 Examples of CYP3A4 inhibitors, inducers and substrates that interact with DEPO-MEDROL

	CYP3A4 Inhibitor	CYP3A4 Inducers	CYP3A4 Substrates
Antibiotics/Antifungal Agents			
• Triacetyloleandomycin	✓		✓
• Erythromycin	✓		✓
• Ketoconazole	✓		✓
• Itraconazole	✓		✓
Antibiotics/Antitubercular Agents			
• Rifampicin		✓	
• Rifabutin		✓	
• Isoniazid (also see Table 2)	✓		
Anticonvulsants			
• Carbamazepine		✓	✓
• Phenobarbital		✓	
• Phenytoin		✓	
Antiemetics			
• Aprepitant	✓		✓
• Fosaprepitant	✓		✓
Antivirals			
• HIV Protease Inhibitors e.g., indinavir and ritonavir	✓		✓
Calcium Channel Blocker			
• Diltiazem	✓		✓
Contraceptives (Oral)			
Ethinylestradiol	✓		✓
• Norethindrone	✓		✓
• Grapefruit Juice	✓		
Immunosuppressants			
• Ciclosporin (also see Table 2)	✓		✓
• Cyclophosphamide			✓
• Tacrolimus			✓
Macrolide Antibacterial Agents			
• Clarithromycin	✓		✓
• Erythromycin	✓		✓
• Troleandomycin	✓		

Table 2 Important drug or substance interactions/effects with methylprednisolone

Class of Drug/Drug(s) Involved	Drug(s) Affected/Mechanism/Clinical Implication
Antibiotic/Antifungal Therapy - Triacetyloleandomycin - Erythromycin - Ketoconazole	CYP3A4 inhibitor. Co-administration may result in reduced corticosteroid clearance, enhanced clinical effects and an increased risk of adverse effects of methylprednisolone.
Antibiotics/Antitubercular therapy - Rifampicin	CYP3A4 inducer. Increased hepatic clearance which may reduce efficacy of corticosteroid. Dosage adjustment may be required.
Anticholinesterase - Neostigmine - Pyridostigmine	Corticosteroids may reduce the effects of anticholinesterases in myasthenia gravis which may result in precipitation of myasthenic crisis.
Anticoagulants - Oral anticoagulants or heparin	Effect on anticoagulant is variable. Enhanced as well as diminished effects of anticoagulants with co-administration with corticosteroids have been reported. Coagulation indices should be monitored. Adjust dose accordingly to maintain desired anticoagulant effects.
Anticonvulsants - Phenobarbitone - Phenytoin	CYP3A4 inducers. Co-administration may increase clearance of methylprednisolone leading to reduced methylprednisolone efficacy. Monitor clinical response. Adjust dose if necessary.
Antidiabetic Drugs - Insulin - Glibenclamide - Metformin	Diabetogenic effects of corticosteroid may impair glucose control of the antidiabetic agents. Monitor glucose levels and adjust dose of antidiabetic therapy if used concurrently with corticosteroids.
All Antihypertensive Agents	Antihypertensive agents are affected with co-administration due to mineralocorticoid effect of corticoid leading to raised blood pressure. May result in partial loss of hypertensive control.
Antitubercular Agents - Isoniazid	CYP3A4 inhibitor. In addition there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Aromatase Inhibitors - Aminoglutethimide	Aminoglutethimide induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Cardioactive Drugs - Digoxin and related glycosides	Corticosteroid induced potassium loss (mineralocorticoid effect). Potentiation of digoxin toxicity.
Diuretic - All potassium losing diuretics e.g., frusemide, thiazide - Carbonic anhydrase inhibitors e.g., acetazolamide	Excessive potassium loss may be experienced with concurrent use of corticosteroids and potassium depleting diuretics or carbonic anhydrase inhibitors. There is enhanced toxicity with co-administration and an increased risk of hypokalaemia. Monitor K+ levels and supplement if necessary.

Class of Drug/Drug(s) Involved	Drug(s) Affected/Mechanism/Clinical Implication
HIV Protease Inhibitors - e.g., indinavir, ritonavir	Co-administration may increase plasma concentrations of corticosteroids. Corticosteroids may reduce plasma concentrations of HIV-protease inhibitors, by inducing their metabolism.
Immunising Agents - Live vaccine e.g., poliomyelitis, BCG, mumps, measles, rubella, smallpox	Co-administration may result in corticosteroid induced immunosuppression. There may be an increased toxicity from vaccine. Disseminated viral disease may occur (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).
- Killed Virulent Vaccines	Co-administration may result in impaired immune response and/or reduced response to vaccine (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).
Immunosuppressants - Methotrexate - Ciclosporin	Synergistic effect on disease state. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse events associated with the individual use of either drug may be more likely to occur. May allow reduced dose of corticosteroid. Increased activity of both ciclosporin and corticosteroids with co-administration. Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin. Monitor ciclosporin A levels. Adjust dose as necessary.
Anticholinergics - Neuromuscular Blocking Agent e.g., Pancuronium, Vecuronium	Partial reversal of neuromuscular block. Acute myopathy has been reported with concurrent use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking agents (see Section 4.4 Special warnings and precautions for use). Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This reaction may be expected with all competitive neuromuscular blockers.
Potassium Depleting Agents - Diuretics - Amphotericin B, xanthines or beta 2 agonists	When administered with potassium depleting agents, patients should be observed closely for development of hypokalaemia as there is an increased risk with concurrent use.
Psychotherapeutic - CNS active drugs such as Anxiolytics and Antipsychotics	Co-administration may potentiate CNS effects of corticosteroid. As the CNS active drug is affected with co-administration, recurrence or poor control of CNS symptoms may result. May require dose adjustment to obtain desired effect.

Class of Drug/Drug(s) Involved	Drug(s) Affected/Mechanism/Clinical Implication
NSAIDs - Aspirin	There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.
Sympathomimetic Agents - Salbutamol	Co-administration leading to increased response to sympathetic agents with resulting increased efficacy and potentially increased toxicity.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

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

Use in Pregnancy – Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal experiments, corticosteroids (such as methylprednisolone) have been shown to increase the incidence of fetal malformations of various kinds (cleft palate, ventricular septal defect, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), intra-uterine growth retardation and abortions. There is limited data on the use of methylprednisolone acetate in human pregnancies, and animal reproduction studies have not been done. Methylprednisolone acetate should be used in pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Corticosteroids readily cross the placenta. Increased incidence of reduced placental and birth weight has been recorded in infants born of mothers receiving corticosteroids.

Infants exposed *in utero* to substantial doses of corticosteroids must be carefully observed and evaluated for signs of adrenal insufficiency. Since the possibility of suppression of the adrenal cortex in the newborn baby after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the fetus when prescribing corticosteroids.

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

The short-term use of corticosteroids antepartum for the prevention of respiratory distress syndrome does not seem to pose a risk to the fetus or the newborn infant. Maternal pulmonary oedema has been reported with tocolysis and fluid overload. No effect is known relating to use in labour and delivery.

Use in Lactation

Corticosteroids are excreted in breast milk.

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Serious undesirable adverse events are also mentioned under the subheading "4.4 Special warnings and precautions for use".

Administration by other than indicated routes has been associated with reports of serious medical events including arachnoiditis, meningitis, paraparesis/paraplegia, sensory disturbances, headache, functional gastrointestinal disorder/bladder dysfunction, seizures, visual impairment including blindness, ocular and periocular inflammation, and residue or slough at injection site.

The adverse effects are listed in the table below by system organ class.

Infections and Infestations

Opportunistic infection, infection[a], peritonitis[b], injection site infection[c].

Blood and Lymphatic System Disorders

Leucocytosis.

Immune System Disorders

Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction.

Endocrine Disorders

Cushingoid, hypothalamic-pituitary-adrenal axis suppression, steroid withdrawal syndrome, adrenal insufficiency.

Metabolism and Nutrition Disorders

Metabolic acidosis, sodium retention, fluid retention, alkalosis hypokalaemic, dyslipidaemia, glucose tolerance impaired[d], increased insulin requirement (or oral hypoglycaemic agents in diabetics), lipomatosis, increased appetite (which may result in weight increased).

Psychiatric Disorders

Affective disorder (including depressed mood, euphoric mood, affect lability, drug dependence, suicidal ideation), psychotic disorder (including mania, delusion, hallucination

and schizophrenia), mental disorder, personality change, confusional state, anxiety, mood swings, abnormal behaviour, insomnia, irritability.

Nervous System Disorders

Epidural lipomatosis, intracranial pressure increased (with papilloedema [benign intracranial hypertension]), seizure, amnesia, cognitive disorder, dizziness, headache.

Eye Disorders

Chorioretinopathy, blindness[e], cataract, glaucoma, exophthalmos, vision blurred.

Ear and Labyrinth Disorders

Vertigo.

Cardiac Disorders

Cardiac failure congestive (in susceptible patients).

Vascular Disorders

Thrombosis, hypertension, hypotension, flushing.

Respiratory, Thoracic and Mediastinal Disorders

Pulmonary embolism, hiccups.

Gastrointestinal Disorders

Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage), intestinal perforation, gastric haemorrhage, pancreatitis, oesophagitis ulcerative, oesophagitis, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea.

Skin and Subcutaneous Tissue Disorders

Angioedema, hirsutism, petechiae, ecchymosis, subcutaneous atrophy, skin atrophy, erythema, hyperhidrosis, skin striae, rash, pruritus, urticaria, acne, skin hyperpigmentation, skin hypopigmentation.

Musculoskeletal and Connective Tissue Disorders

Muscular weakness, myalgia, myopathy, rhabdomyolysis, muscle atrophy, osteoporosis, osteonecrosis, pathological fracture, neuropathic arthropathy, arthralgia, growth retardation, post injection pain flare (following intra-articular, periarticular and tendon sheath injections)[f].

Reproductive System and Breast Disorders

Menstruation irregular.

General Disorders and Administration Site Conditions

Abscess sterile, impaired healing, oedema peripheral, fatigue, malaise, injection site reaction.

Investigations

Intraocular pressure increased, carbohydrate tolerance decreased, blood potassium decreased, urine calcium increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, suppression of reactions to skin tests[f].

Injury, Poisoning and Procedural Complications

Spinal compression fracture, tendon rupture.

[a] Including masking of infections and latent infections becoming active.

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

[c] Following non-sterile administration (see Section 4.4 Special warnings and precautions for use).

[d] Manifestations of latent diabetes mellitus.

[e] Rare instances of blindness associated with intralesional therapy around the face and head.

[f] Not a MedDRA Preferred Term.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/safety/reporting-problems.

4.9 Overdose

Reports of acute toxicity and metabolic disturbances with glucocorticoids are rare but do occur. There is no clinical syndrome of acute overdosage with DEPO-MEDROL (methylprednisolone acetate). Acute overdose may possibly aggravate pre-existing disease states such as ulceration of the gastrointestinal tract, electrolyte disturbances, infections, diabetes and oedema. Repeated high doses of methylprednisolone have caused hepatic necrosis and an increase in amylase. Bradyarrhythmias, ventricular arrhythmias and cardiac arrest have been observed in cases of intravenous administration of high doses of methylprednisolone.

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

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.

DEPO-MEDROL contains Macrogol (polyethylene glycol) as an excipient. Hypokalaemia has been reported following an unintentional large intravenous administration of Macrogol. In case of overdose, monitor acid-balance; renal, cardiac and pulmonary function in symptomatic patients and treat accordingly. Onset of acute lung injury may be delayed.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Naturally occurring glucocorticoids (hydrocortisone), which also have salt-retaining properties, are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogues are used primarily for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

Clinical Trials

No data available.

5.2 Pharmacokinetic properties

No data available.

5.3 Preclinical safety data

Genotoxicity

Methylprednisolone acetate has not been formally evaluated for genotoxicity. However, methylprednisolone sulfonate, which is structurally similar to methylprednisolone, was not mutagenic in bacteria (*Ames* test), or in a mammalian cell gene mutation assay using Chinese hamster ovary cells. Methylprednisolone suleptanate did not induce unscheduled DNA synthesis in primary rat hepatocytes. Prednisolone farnesylate, which is also structurally similar to methylprednisolone, was not mutagenic in bacteria, but displayed weak clastogenic activity *in vitro* in Chinese hamster lung fibroblasts in the presence of metabolic activation.

Carcinogenicity

Methylprednisolone has not been formally evaluated in rodent carcinogenicity studies. Negative results for carcinogenicity have been obtained with various other glucocorticoids including budesonide, prednisolone and triamcinolone acetonide, in mice. However, all three of these compounds were shown to increase the incidence of hepatocellular adenomas and carcinomas after oral administration in a 2-year study in male rats. These tumorigenic effects occurred at doses that are less than the typical clinical doses on a mg/m^2 basis. Hepatocarcinogenicity is likely to involve an interaction with the glucocorticoid receptor.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each mL contains:

Macrogol 3350	29 mg
Sodium chloride	8.7 mg

Miripirium chloride (added as preservative)	0.195 mg
Water for injections	QS

When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid. The pH of the finished product remains within the USP specified range, i.e., 3.0 to 7.0.

6.2 Incompatibilities

Because of possible physical incompatibilities, DEPO-MEDROL should not be diluted or mixed with other solutions.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

DEPO-MEDROL is for single use in a single patient only. Discard any unused product.

Store below 30°C. Protect from freezing.

6.5 Nature and contents of container

DEPO-MEDROL Suspension for Injection is available in single dose glass vials and supplied in pack sizes of 5 x 1 mL and 1 x 1 mL vials.

Not all presentations are marketed.

6.6 Special precautions for disposal

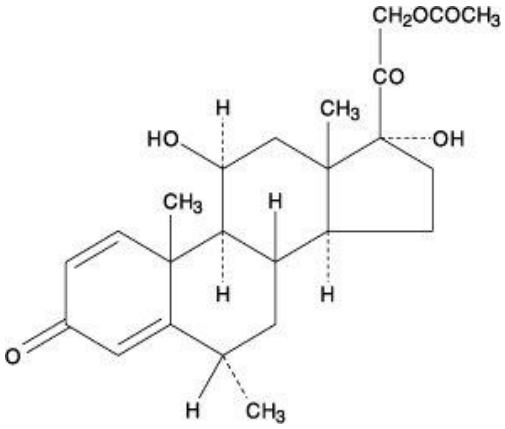
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Methylprednisolone acetate is a 6-methyl derivative of prednisolone.

Methylprednisolone acetate is a white or practically white, odourless, crystalline powder which melts at about 215°C with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol, and slightly soluble in ether. It is practically insoluble in water.

Chemical Structure



Chemical name:	11β, 17α, 21-trihydroxy-6α-methylpregna-1,4-diene-3,20-dione acetate
Molecular Formula	$C_{24}H_{32}O_6$
Molecular weight:	416.51

CAS Number

53-36-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

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Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

2 August 1991

10. DATE OF REVISION

5 March 2025

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
Throughout	Minor editorial changes.
4.4, 4.8	Addition of warning and ADR on “Rhabdomyolysis”.