

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DEPO-MEDROL[®] 40 mg/mL Suspension for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL vial contains 40 mg/mL methylprednisolone acetate

Excipients with known effects:

- Sodium
- Macrogol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Depo-Medrol is a white, aqueous, sterile suspension.

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:

Endocrine Disorders

- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy; mineralocorticoid supplementation is of particular importance).
- Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).
- Congenital adrenal hyperplasia.
- Hypercalcaemia associated with cancer.
- Nonsuppurative thyroiditis.

Rheumatic Disorders

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

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

Collagen Diseases

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

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

Dermatologic Disease

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

Allergic State

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

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

Ophthalmic Disease

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

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

Gastrointestinal Disease

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

- Ulcerative colitis
- Regional enteritis.

Respiratory Disease

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

Haematologic Disorders

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

Neoplastic Disease

For palliative management of:

- Leukemias and lymphomas
- Acute leukaemia of childhood.

Oedematous States

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

Nervous System

Acute exacerbations of multiple sclerosis.

Miscellaneous

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

B. For Intra-articular or Soft Tissue Administration (including Periarticular and Intrabursal)

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

- Post-traumatic osteoarthritis
- Synovitis of osteoarthritis
- Rheumatoid arthritis
- Acute and subacute bursitis
- Epicondylitis
- Acute nonspecific tenosynovitis
- Acute gouty arthritis.

C. For Intralesional Administration

Depo-Medrol is indicated for intralesional use in the following conditions:

- Keloids, localised hypertrophic, infiltrated, inflammatory lesions of lichen planus, psoriatic plaques, granuloma annular, lichen simplex chronicus (neurodermatitis), discoid lupus erythematosus, Necrobiosis lipoidica diabetorum, alopecia areata.
- Depo-Medrol may also be useful in cystic tumours of an aponeurosis or tendon (ganglia).

D. For Intrarectal Instillation

- Ulcerative colitis.

4.2 Dose and method of administration

Dose

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.

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

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Sterile technique is necessary to prevent infections or contamination.

Depo-Medrol may be used by any of the following routes: intramuscular, intra-articular, periarticular, intrabursal, intralesional and into the tendon sheath. It MUST NOT be used by the intrathecal, epidural or intravenous routes (see sections 4.3, 4.4 and 4.8).

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	20-80 mg
Medium	Elbows, Wrists	10-40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4-10 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 joint space has been entered by the needle.

The injection site for each joint is determined by the 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 occasionally 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 corticosteroid therapy care should be taken to avoid overuse of 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 one percent 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 effect disappearance.

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 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 Effects in Dermatologic Conditions*

Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60 mg of the suspension is injected into the lesion. It may be necessary to distribute doses ranging from 20 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 seven and given as a singular 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. Use in children should be limited to the shortest possible time.

Hormone therapy is 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 GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.

In patients with the adrenogenital syndrome, a single intra-muscular 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 to 120 mg. The usual dosage for patients with dermatologic lesions benefited by systemic corticoid therapy is 40 to 120 mg of methyl-prednisolone acetate administered intramuscularly at weekly intervals for one to four weeks. In acute severe dermatitis due to poison ivy, relief may result within 8 to 12 hours following intramuscular administration of a single dose of 80 mg to 120 mg. In chronic contact dermatitis repeated at five to ten 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 to 120 mg to asthmatic patients, relief may result within six to 48 hours and persist for several days to two weeks. Similarly, in patients with allergic rhinitis (hay fever), an intramuscular dose of 80 to 120 mg may be followed by relief of coryzal symptoms within six hours, persisting for several days to three 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 is indicated.

C. Intrarectal Administration

Depo-Medrol sterile aqueous suspension in doses of 40 to 120 mg administered as retention enemas or by continuous drip three to seven times weekly for periods of two or more weeks, have been shown to be a useful adjunct in the treatment of some patients with ulcerative colitis. Many patients can be controlled with 40 mg of Depo-Medrol sterile aqueous suspension administered in from 30-300 mL of water depending upon the degree of involvement of the inflamed colonic mucosa. Other accepted therapeutic measures should, of course, be instituted.

4.3 Contraindications

Known hypersensitivity to methylprednisolone or any component of the formulation.

Systemic fungal infections.

Intrathecal administration due to its potential for neurotoxicity.

Epidural administration.

Intravenous administration as the product is a suspension.

It MUST NOT be used by the intrathecal, epidural, intravenous or any other unspecified routes.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see section 4.4, **Immunosuppressive 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 should 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 physiochemical 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.

Depo-Medrol should not be administered by any route other than those listed under Section 4.1. It is critical that, during administration of Depo-Medrol, appropriate technique be used and care taken to assure proper placement of the medicine.

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

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 increase susceptibility to infection, may mask some signs of infection, which may reach an advanced stage before the infection is recognised, 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. Caution must therefore be exercised in patients with HIV/AIDS or diabetes.

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

Depo-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, their routine use in septic shock is not recommended and 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. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such

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

The use of methylprednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with 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.

Immune System Effects

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

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

Endocrine Effects

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.

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. Therefore, withdrawal of corticosteroid should always be gradual.

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. 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 reinstated.

A steroid “withdrawal syndrome”, seemingly unrelated to adrenocortical insufficiency, may 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.

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

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.

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 diabetes mellitus or a family history of diabetes mellitus.

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

Potentially severe psychiatric adverse reactions may occur with systemic corticosteroids (see section 4.8). 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.

Nervous System Effects

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

Corticosteroids should be used with caution in patients with myasthenia gravis (see section 4.4, **Musculoskeletal Effects**).

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see section 4.2).

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

Ocular Effects

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.

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

Cardiac Effects

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects if high doses and/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.

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

Vascular Effects

Corticosteroids should be used with caution in patients with hypertension.

Gastrointestinal Effects

High doses of corticosteroids may produce acute pancreatitis.

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. 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, oesophagitis and gastritis.

Hepatobiliary Effects

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

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.

Musculoskeletal Effects

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 generalised, 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 a common but infrequently recognised 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 be used with caution in patients with previous steroid myopathy.

Renal and Urinary Disorders

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.

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 (see section 4.4, Endocrine Effects)

Injury, Poisoning and Procedural Complications

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

Other

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see section 4.5, **Other Interactions, NSAIDs**).

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 motion, 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 (see section 4.2).

Sterile technique is necessary to prevent infections or contamination.

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

Paediatric Use

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. 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 restricted to the most serious indications. Use in children should be limited to the shortest possible time.

Increased intracranial pressure with papilloedema (pseudotumour cerebri) in children has been reported, usually after treatment withdrawal of methylprednisolone. Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

Use in the Elderly

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.

4.5 Interaction with other medicines and other forms of interaction

The pharmacokinetic interactions listed below are potentially clinically important.

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is metabolised mainly by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyses 6 β -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 medicines) 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. Coadministration of CYP3A4 inhibitors may require titration of methylprednisolone dosage to reduce the risk of adverse effects and avoid steroid toxicity.

CYP3A4 inhibitors include:

- Antifungals such as ketoconazole and itraconazole.
- Antiemetics such as aprepitant and fosaprepitant.
- Immunosuppressants such as ciclosporin. Mutual inhibition of metabolism occurs with concurrent use of ciclosporin and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon coadministration. Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin.
- Macrolide antibacterials such as clarithromycin, erythromycin and troleanomycin.
- HIV-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.
- Calcium channel blockers such as diltiazem.
- Isoniazid may increase the plasma concentration of methylprednisolone. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
- Oral contraceptives such as ethinylestradiol and norethisterone, 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.
- Grapefruit juice.

CYP3A4 Inducers

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

CYP3A4 inducers include:

- Anticonvulsants such as phenobarbital, phenytoin, carbamazepine and primidone.
- Bactericidal antibiotics such as rifampicin and rifabutin.

CYP3A4 Substrates

In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration. Most CYP3A4 inhibitors are also CYP3A4 substrates.

- Immunosuppressants such as cyclophosphamide and tacrolimus.

Other Interactions

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

Antidiabetic Agents

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

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 (see section 4.4, **Musculoskeletal Effects**).

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.

Anticholinesterases

Steroids may reduce the effects of anticholinesterases in myasthenia gravis

Anticoagulants (Oral)

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.

Aromatase Inhibitors

Aminogluethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

Cardiac Glycosides

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

Diuretics and Other Potassium Depleting Agents

Excessive potassium loss maybe experienced with concurrent use of corticosteroids and potassium depleting diuretics (such as frusemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide). Patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists.

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 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.

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.

Vaccines

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Some animal studies have shown that corticosteroids (such as methylprednisolone), have been shown to increase the incidence of foetal malformations of various kinds (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), and intra-uterine growth retardation. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women.. Since adequate human reproductive studies have not been done with methylprednisolone acetate, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Corticosteroids readily cross the placenta. An increased incidence of low-birth weights in infants born of mothers receiving corticosteroids has been reported. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses.

Infants born to mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency, although neonatal adrenal insufficiency is rarely reported in infants exposed *in utero* to corticosteroids.

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

Labour and Delivery

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

Breast-feeding

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.

Effects on fertility

Corticosteroids have been shown to impair fertility in animal studies. Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced.

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 Undesirable effects

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 and frequency.

Infections and Infestations

Not known: Opportunistic infection, infection^a, peritonitis^f, oesophageal candidiasis, injection site infection^b.

Blood and Lymphatic System Disorders

Not known: Leucocytosis.

Immune System Disorders

Not known: Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction.

Endocrine Disorders

Not known: Cushingoid, hypopituitarism, steroid withdrawal syndrome.

Metabolism and Nutrition Disorders

Not known: Metabolic acidosis, , sodium retention, fluid retention, alkalosis hypokalaemic, , dyslipidaemia, glucose tolerance impaired^c, increased insulin requirement (or oral hypoglycaemic agents in diabetics), lipomatosis, increased appetite (which may result in weight increased).

Psychiatric Disorders

Not known: Affective disorder (including depressed mood, euphoric mood, affect lability, drug dependence, suicidal ideation), psychotic disorder (including mania, delusion, hallucination and schizophrenia), psychotic behaviour, mental disorder, personality change, confusional state, anxiety, mood swings, abnormal behaviour, insomnia, irritability.

Nervous System Disorders

Not known: Epidural lipomatosis, intracranial pressure increased (with papilloedema [benign intracranial hypertension]), seizure, amnesia, cognitive disorder, dizziness, headache.

Eye Disorders

Not known: Chorioretinopathy, blindness^d, cataract, glaucoma, exophthalmos, corneal thinning, scleral thinning, exacerbation of ophthalmic viral or fungal disease.

Ear and Labyrinth Disorders

Not known: Vertigo.

Cardiac Disorders

Not known: Cardiac failure congestive (in susceptible patients).

Vascular Disorders

Not known: Thrombosis, hypertension, hypotension.

Respiratory, Thoracic and Mediastinal Disorders

Not known: Pulmonary embolism, hiccups.

Gastrointestinal Disorders

Not known: 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

Not known: Angioedema, hirsutism, petechiae, ecchymosis, subcutaneous atrophy, skin atrophy, erythema, hyperhidrosis, skin striae, rash, pruritus, urticaria, telangiectasia, acne, skin hyperpigmentation, skin hypopigmentation.

Musculoskeletal and Connective Tissue Disorders

Not known: Muscular weakness, myalgia, myopathy, muscle atrophy, osteoporosis, osteonecrosis, pathological fracture, neuropathic arthropathy, arthralgia, growth retardation.

Reproductive System and Breast Disorders

Not known: Menstruation irregular, amenorrhoea.

General Disorders and Administration Site Conditions

Not known: Abscess sterile, impaired healing, oedema peripheral, , fatigue, malaise, , injection site reaction, post-injection flare^e.

Investigations

Not known: Intraocular pressure increased, carbohydrate tolerance decreased, blood potassium decreased, , calcium balance negative, urine calcium increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, suppression of reactions to skin tests^g.

Injury, Poisoning and Procedural Complications

Not known: Spinal compression fracture, tendon rupture.

^a Including increased susceptibility to and severity of infections, masking of infections and latent infections (e.g. tuberculosis) becoming active.

^b Following non-sterile administration.

^c Manifestations of latent diabetes mellitus.

^d Rare instances of blindness associated with intralesional therapy around the face and head.

^e Following intra-articular use.

^f Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).

^g Not a MedDRA preferred term.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

There is no clinical syndrome of acute overdosage with Depo-Medrol (methylprednisolone acetate).

Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state, and other complications of chronic steroid therapy.

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 dialysable.

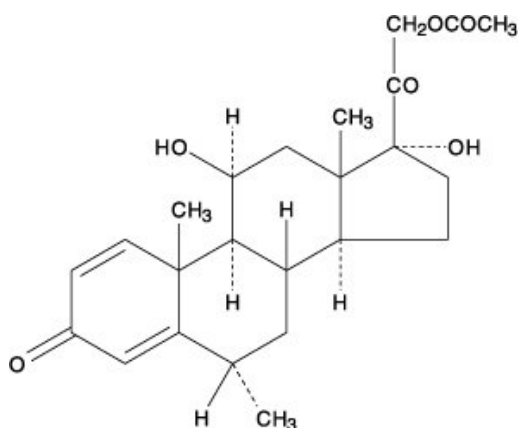
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-,(6 α ,11 β).

The structural formula is shown below:



Molecular formula: $C_{24}H_{32}O_6$

Molecular weight: 416.51

CAS Registry Number: 53-36-1.

Methylprednisolone is an anti-inflammatory steroid. Estimates of the relative potencies of methylprednisolone relative to prednisolone range from 1.13 to 2.1 with an average of 1.5. In general the required daily dose of methylprednisolone can be estimated to be two thirds (or 0.7) the required daily dose of prednisolone. While the effect of parenterally administered methylprednisolone acetate is prolonged, it has the same metabolic and anti-inflammatory actions as orally administered medicine.

Cortisol and its synthetic analogues, such as methylprednisolone acetate, exert their action locally by preventing or suppressing the development of local heat, redness, swelling and tenderness by which inflammation is recognized at the gross level of observation. At the microscopic level, such compounds inhibit not only the early phenomena of the inflammatory process (oedema, fibrin deposition, capillary dilation, migration of phagocytes into the inflamed areas and phagocytic activity), but also the later manifestations (capillary proliferation, fibroblast proliferation, deposition of collagen and still later cicatrisation). These compounds inhibit inflammatory response whether the inciting agent is mechanical, chemical or immunological.

5.2 Pharmacokinetic properties

Absorption

Methylprednisolone acetate is hydrolysed to its active form by serum cholinesterases. The intracellular activity of glucocorticoids results in a clear difference between plasma half-life and pharmacological half-life. Pharmacological activity persists after measurable plasma levels have disappeared.

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

Intramuscular (I.M.) injections of 40 mg/mL give after approximately 7.3 ± 1 hour (T_{max}) methylprednisolone serum peaks of 1.48 ± 0.86 mcg/100 mL (C_{max}). The half-life is in this case 69.3 hours. After a single I.M. injection of 40 to 80 mg methylprednisolone acetate, duration of HPA axis suppression ranged from 4 to 8 days. An intra-articular injection of 40 mg in both knees (total dose: 80 mg) gives after 4 to 8 hours methylprednisolone peaks of approximately 21.5 mcg/100 mL.

Distribution

After intra-articular administration methylprednisolone acetate diffuses from the joint into systemic circulation over approximately 7 days, as demonstrated by the duration of the HPA axis suppression and by the serum methylprednisolone values.

In man, methylprednisolone forms a weak dissociable bond with albumin and transcortin. Approximately 40 to 90% of the drug is bound.

Biotransformation or Metabolism

Metabolism of methylprednisolone occurs via hepatic routes qualitatively similar to that of cortisol. The major metabolites are 20 beta-hydroxymethylprednisolone and 20 beta-hydroxy-6-alpha-methylprednisone. The metabolites are mainly excreted in the urine as glucuronides, sulphates and unconjugated compounds. These conjugation reactions occur principally in the liver and to some extent in the kidney.

5.3 Preclinical safety data

Genotoxicity

Methylprednisolone has not been formally evaluated for genotoxicity. However, methylprednisolone sulfonate, which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* at 250 to 2,000 µg/plate, or in a mammalian cell gene mutation assay using Chinese hamster ovary cells at 2,000 to 10,000 µg/mL. Methylprednisolone sulfonate did not induce unscheduled DNA synthesis in primary rat hepatocytes at 5 to 10,000 µg/mL. Moreover, a review of published data indicates that prednisolone farnesylate (PNF), which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* and *Escherichia coli* strains at 312 to 5,000 µg/plate. In a Chinese hamster fibroblast cell line, PNF produced a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested 1,500 µg/mL.

Carcinogenicity

Methylprednisolone has not been formally evaluated in rodent carcinogenicity studies. Variable results have been obtained with other glucocorticoids tested for carcinogenicity in mice and rats. However, published data indicate that several related glucocorticoids including budesonide, prednisolone, and triamcinolone acetonide can increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water to male rats. These tumorigenic effects occurred at doses which were less than the typical clinical doses on a mg/m² basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Macrogol 3350
Miripirium chloride (0.02%) as a preservative
Sodium chloride
Sodium hydroxide
Water for injection

6.2 Incompatibilities

Because of possible physical incompatibilities, Depo-Medrol sterile aqueous suspension (methylprednisolone acetate) should not be diluted or mixed with other solutions.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C.

Depo-Medrol is for single use in a single patient only. Discard any unused product.

6.5 Nature and contents of container

40 mg/mL – 1 x 1 mL vial; 5 x 1 mL

6.6 Special precautions for disposal and other handling

No special requirement.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Ltd
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

16 June 1976

10. DATE OF REVISION OF THE TEXT

12 February 2018.

® Depo-Medrol is a registered trademark of Pfizer Inc.

Summary of table of changes

Section	Update
All	Reformatted in line with EU SPC format
Section 4.4	Addition of a cautionary statement about use in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone.