

# Depo-Medrol<sup>®</sup>

## Methylprednisolone acetate

40 mg/mL injection

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## PRESENTATION

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Depo-Medrol is a white aqueous sterile suspension containing Methylprednisolone acetate USP 40 mg/mL in a 1 mL vial.

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## USES

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### **Actions**

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.

### **Pharmacokinetics**

#### *Absorption*

Methylprednisolone acetate is hydrolysed to its active form by serum cholinesterases. In man, methylprednisolone forms a weak dissociable bond with albumin and transcortin. Approximately 40 to 90% of the drug is bound. 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.

I.M. injections of 40mg/mL give after approximately  $7.3 \pm 1$  hour ( $T_{max}$ ) methylprednisolone serum peaks of  $1.48 \pm 0.86$  mcg/100 mL ( $C_{max}$ ). The half-life is in this case 69.3 hours. After a single I.M. injection of 40 to 80mg 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: 80mg) 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.

### ***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-methyl-prednisone. 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.

## **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.
- Hypercalcemia 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 edema (epinephrine 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-synovial 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.

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## DOSAGE AND ADMINISTRATION

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

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

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

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 discoloration 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 or intravenous routes (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS and ADVERSE EFFECTS).**

### 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	20-80mg
Medium	Elbows, Wrists	10-40mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4-10mg

## ***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, epiconylitis***

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 usual sterile precautions should be observed, of course, with each injection.

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 30mg. In recurrent or chronic conditions, repeated injections may be necessary.

#### ***4. Injections for local effects in dermatologic conditions***

Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60mg of the suspension is injected into the lesion. It may be necessary to distribute doses ranging from 20 to 40mg 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 40mg every two weeks may be adequate. For maintenance of patients with rheumatoid arthritis, the weekly intramuscular dose will vary from 40 to 120mg. The usual dosage for patients with dermatologic lesions benefited by systemic corticoid therapy is 40 to 120mg 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 80mg to 120mg. In chronic contact dermatitis repeated at five to ten day intervals

may be necessary. In seborrhoeic dermatitis, a weekly dose of 80mg may be adequate to control the condition.

Following intramuscular administration of 80 to 120mg 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 120mg 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 120mg 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 40mg of Depo-Medrol sterile aqueous suspension administered in from 30-300mL of water depending upon the degree of involvement of the inflamed colonic mucosa. Other accepted therapeutic measures should, of course, be instituted.

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## CONTRAINDICATIONS

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Known hypersensitivity to components.

Systemic fungal infections.

Intrathecal administration due to its potential for neurotoxicity.

Intravenous administration as the product is a suspension.

**It MUST NOT be used by the intrathecal or intravenous routes.**

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## WARNINGS AND PRECAUTIONS

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

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

## **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 mask some signs of infection, which may reach an advanced stage before the infection is recognised. There may be decreased resistance and inability to localise infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humeral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of cortico-steroids, the rate of occurrence of infectious complications increases. Caution must therefore be exercised in patients with HIV/AIDS or diabetes.

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 immunization 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.

### **Blood and Lymphatic System**

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

### **Hypersensitivity reactions**

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

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

### ***Endocrine***

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

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

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

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

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

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

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

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

Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes and predisposes those on long term corticosteroid therapy to diabetes mellitus, therefore, corticosteroids should be used in patients with, or a family history of diabetes mellitus.

### ***Psychiatric***

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Therefore, particular care is required when considering the use of corticosteroids in patients with existing or previous history of severe affective disorders.

Symptoms of potentially severe psychiatric adverse reactions associated with corticosteroids use typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

Psychological effects have also been reported upon withdrawal of corticosteroids; the frequency is unknown.

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

### ***Nervous System***

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

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

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

### ***Ocular***

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

Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure may result in glaucoma with possible damage to the optic nerves. Establishment of secondary ocular infections due to fungi or viruses of the eye may also be enhanced in patients receiving glucocorticoids.

### ***Cardiovascular***

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

Corticosteroids should be used with caution in patients with hypertension.

### ***Gastrointestinal***

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

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

### ***Hepatobiliary***

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

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

### ***Musculoskeletal***

Corticosteroids should be used with caution in patients with myasthenia gravis who are receiving anticholinesterase therapy as corticosteroid use may decrease plasma anticholinesterase activity. An acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g, myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g, pancuronium). This acute myopathy is generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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

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

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

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

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

### ***Investigations***

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

### ***Discontinuation***

A steroid "withdrawal syndrome", seemingly unrelated to adrenocortical insufficiency, may occur following abrupt discontinuance of glucocorticoids. These effects are thought to be due to the

sudden change in glucocorticoid concentration rather than to low corticosteroid levels (see **Adverse Events, General disorders and administration site conditions**)

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

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

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-synovial and intramuscular injection should include precautions against injection or leakage into the dermis.

### ***Other***

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.

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

### ***THE FOLLOWING ADDITIONAL PRECAUTIONS APPLY FOR PARENTERAL CORTICOSTEROIDS***

The following additional precautions apply for parenteral corticosteroids. Intra-synovial 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.

Sterile technique is necessary to prevent infections or contamination.

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

Because rare instances of anaphylactic 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.

Corticosteroids should not be injected into unstable joints.

### ***Carcinogenicity, Mutagenicity, Impairment of fertility***

No evidence exists showing that corticosteroids are carcinogenic, mutagenic or impair fertility.

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

#### ***Pregnancy***

Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause foetal malformations. Adequate human reproductive studies have not been done with corticosteroids. Therefore the use of this drug in pregnancy, nursing mothers, or women of child bearing potential requires that the benefits of the drug be carefully weighed against the potential risk to the mother and embryo or foetus. Since there is inadequate evidence of safety in human pregnancy, this drug should be used in pregnancy only if clearly needed.

Corticosteroids readily cross the placenta. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency.

Labour and Delivery There are no known effect of corticosteroids on labour and delivery.

Lactation Corticosteroids are excreted in breast milk, therefore the potential benefit of treatment must be weighed against the potential hazards to the infant.

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

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

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

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

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

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

## ADVERSE EFFECTS

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

<b>Vascular disorders</b>	Hypertension Hypotension
<b>Cardiac disorders</b>	Heart failure congestive (in susceptible patients)
<b>Musculoskeletal and connective tissue disorders</b>	Arthralgia Growth retardation Muscular atrophy Muscular weakness Myalgia Steroid myopathy Avascular osteonecrosis Neuropathic arthropathy Osteoporosis Pathologic fractures
<b>Gastrointestinal disorders</b>	Abdominal distension Abdominal pain Diarrhoea Dyspepsia Nausea Oesophagitis Peptic ulcer with possible perforation Peptic ulcer haemorrhage Pancreatitis Gastric haemorrhage Intestinal perforation Oesophageal ulcerative Oesophageal candidiasis
<b>Investigations</b>	Alanine transaminase increased Aspartate transaminase increased Blood alkaline phosphatase increased Blood potassium decreased Carbohydrate tolerance decreased Increased calcium excretion/Urine calcium increased.
<b>Skin and subcutaneous tissue disorders</b>	Angioedema Ecchymosis Erythema Hirsutism Hyperhidrosis Petechiae

	<p>Pruritus Rash Skin atrophy, striae, urticaria, Impaired wound healing Acne Telangiectasia Thin fragile skin</p>
<b>Psychiatric disorders</b>	<p>Abnormal behaviour Affective disorder (including affect lability, depressed mood, euphoric mood, psychological dependence, suicidal ideation) Behavioural disturbances (including anxiety, confusional state, insomnia, irritability) Mental disorder Mood swings Personality change Psychotic behaviour Psychotic disorders (including mania, delusion, hallucination and schizophrenia [aggravation of])</p>
<b>Nervous system disorders</b>	<p>Amnesia Cognitive disorder Dizziness Headache Convulsions Intracranial pressure increased (with papilloedema [benign intracranial hypertension])</p>
<b>Endocrine disorders</b>	<p>Cushingoid symptoms Hypopituitarism Manifestation of latent diabetes Suppression of growth in infants, children and adolescents</p>
<b>Reproductive system and breast disorders</b>	<p>Menstruation irregularities and amenorrhoea</p>
<b>Metabolism and nutrition disorders</b>	<p>Alkalosis hypokalaemic Fluid retention, Increased appetite (which may result in weight gain), increased requirements for insulin or oral hypoglycaemic agents in diabetics Metabolic acidosis Sodium retention Negative nitrogen and calcium balance</p>
<b>Eye disorders</b>	<p>Cataract subcapsular Glaucoma Exophthalmos Intraocular pressure increased Corneal or scleral thinning Exacerbation of ophthalmic viral or fungal disease</p>
<b>Ear and labyrinth disorders</b>	<p>Vertigo</p>

<b>Infections and Infestations</b>	Masking of infection, latent infection becoming active Opportunistic infections, Recurrence of latent tuberculosis
<b>Immune system disorders</b>	Drug hypersensitivity (including anaphylactic reaction and anaphylactoid reaction) Suppression of reactions to skin tests
<b>General disorders and administration site conditions</b>	Fatigue, impaired healing, malaise, leucocytosis  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.
<b>Injury, poisoning and procedural complications</b>	Long bone and spinal compression fracture Tendon rupture (particularly of the Achilles tendon)

The following additional reactions are related to parenteral corticosteroid therapy:

- Rare instances of blindness associated with intralesional therapy around the face and head
- Anaphylactic reaction or allergic reactions
- Hyperpigmentation or hypopigmentation
- Subcutaneous and cutaneous atrophy
- Sterile abscess
- Post-injection flare, following intra-synovial use
- Charcot-like arthropathy
- Injection site infections following non-sterile technique

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## **INTERACTIONS**

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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 $\beta$ -hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

### ***CYP3A4 INHIBITORS***

Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance, resulting in increased plasma concentration of methylprednisolone. These include:

- Antifungals such as ketoconazole and itraconazole
- Antiemetics, such as aprepitant and fosaprepitant
- Immunosuppressants such as cyclosporine
- Macrolide antibacterials such as clarithromycin, erythromycin and troleandomycin
- HIV-Protease inhibitors
- Cyclosporin
- Ritonavir
- Diltiazem
- Grapefruit juice

Coadministration of CYP3A4 inhibitors may require titration of methylprednisolone dosage to reduce the risk of adverse effects and avoid steroid toxicity.

### ***CYP3A4 INDUCERS***

Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentrations of methylprednisolone. These include:

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

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

### ***CYP3A4 SUBSTRATES***

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

### ***OTHER INTERACTIONS***

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

#### ***Antacids***

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

### ***Antidiabetic agents***

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

### ***Oral anticoagulants***

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

### ***Anticholinergics***

Corticosteroids may influence the effect of anticholinergics.

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

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

### ***Cardiac glycosides***

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

### ***Oral contraceptives***

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

### ***Diuretics***

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

### ***Mifepristone***

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

### ***NSAIDs***

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

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

### *Somatropic*

Concomitant administration may inhibit the growth promoting effect of somatropin.

### *Sympathomimetics*

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

### *Antivirals*

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

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

### *Antifungals*

The risk of hypokalaemia may be increased with amphotericin.

### *Vaccines*

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

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## **OVERDOSAGE**

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

Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state.

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## **PHARMACEUTICAL PRECAUTIONS**

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### *Shelf Life*

3 years at store below 30°C.

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## **MEDICINE CLASSIFICATION**

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Prescription Medicine.

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## PACKAGE QUANTITIES

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40 mg/mL – 1 x 1mL vial; 5 x 1 mL

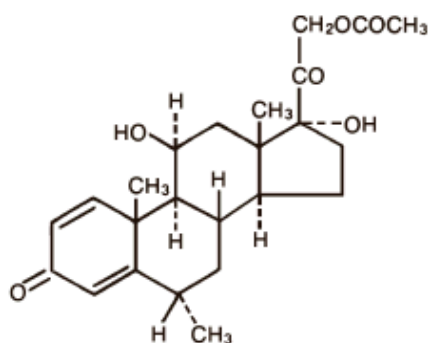
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## FURTHER INFORMATION

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The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-,(6 $\alpha$ ,11 $\beta$ ). The molecular weight is 416.51 and the empirical formula is C<sub>24</sub>H<sub>32</sub>O<sub>6</sub>.

The structural formula is represented below:



The CAS Number is 53-36-1.

Depo-Medrol contains myristy-gamma-picolinium chloride (0.02%) as a preservative.

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## NAME AND ADDRESS

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## DATE OF PREPARATION

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10 January 2012

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