PT. Pfizer Indonesia
Local Product Document

Generic Name: Methylprednisolone Acetate
Trade Name: DEPO-MEDROL®
CDS Effective Date: January 12, 2023
Supersedes: October 22, 2020

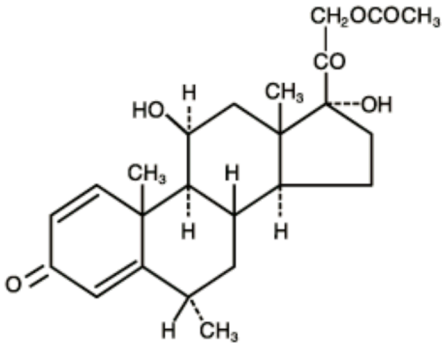
DEPO-MEDROL®
METHYLPREDNISOLONE ACETATE
Brand of methylprednisolone acetate sterile aqueous suspension
(Sterile methylprednisolone acetate suspension)

Not for Intravenous Use

DESCRIPTION

DEPO-MEDROL Sterile Aqueous Suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is a white or practically white, odorless, crystalline powder which melts at 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol, and slightly soluble in ether. It is practically insoluble in water. The chemical name for methylprednisolone acetate is pregna-1, 4-diene-3, 20-dione, 21-(acetyloxy)-11, 17-dihydroxy-6-methyl-, (6α, 11β) - and the molecular weight is 416.51.

The structural formula is represented below:



DEPO-MEDROL is an anti-inflammatory glucocorticoid, for intramuscular, intrasynovial, soft tissue or intralesional injection. It is available in one strength: 40 mg/mL.

PHARMACEUTICAL PARTICULARS

List of Excipients:
Sodium chloride, macrogol 3350, miripirium chloride and water for injection.

ACTIONS

Naturally occurring glucocorticoids (hydrocortisone), which also have salt retaining properties, are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogs are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoid cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

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 Sterile Aqueous Suspension (methylprednisolone acetate) is indicated as follows:

1. 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.

2. 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)
- Epicondylitis
- Acute non-specific tenosynovitis
- Acute gouty arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Acute and subacute bursitis

3. Collagen Diseases

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

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

4. Dermatologic Diseases

- Pemphigus
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Exfoliative dermatitis
- Bullous dermatitis herpetiformis
- Severe seborrheic dermatitis
- Severe psoriasis
- Mycosis fungoides

5. Allergic States

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

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

6. Ophthalmic Diseases

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

7. Gastrointestinal Diseases

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

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

8. Respiratory Diseases

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

9. Hematologic Disorders

- Acquired (autoimmune) hemolytic anemia
- Secondary thrombocytopenia in adults
- Erythroblastopenia (RBC anemia)
- Congenital (erythroid) hypoplastic anemia

10. Neoplastic Diseases

For palliative management of:

- Leukemias and lymphomas
- Acute leukemia of childhood

11. Edematous States

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

12. Miscellaneous

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

B. FOR INTRA-SYNOVIAL OR SOFT TISSUE ADMINISTRATION (including periarticular and intrabursal) SEE WARNINGS

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

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

C. FOR INTRALESIONAL ADMINISTRATION

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

Keloids, Localized hypertrophic, infiltrated, inflammatory lesions of:

- Lichen planus, psoriatic plaques
- Granuloma annulare
- Lichen simplex chronicus (neurodermatitis)
- Discoid lupus erythematosus
- Necrobiosis lipoidica diabeticorum
- Alopecia areata

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

CONTRAINDICATIONS

Methylprednisolone acetate is contraindicated:

- in patients who have systemic fungal infections
- in patients with known hypersensitivity to methylprednisolone or any component of the formulation
- for use by the intrathecal route of administration
- for use by the epidural route of administration
- for use by the intravenous route of administration

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

WARNINGS

Multidose use of DEPO-MEDROL from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. Particular care, such as use of disposable sterile syringes and needles, is necessary.

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

In order to minimize 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. 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.

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

<u>Endocrine Effects</u>

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

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

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

Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

A steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

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

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

Immunosuppressant Effects/Increased Susceptibility to Infections
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

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

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.

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

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

Usage in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of child-bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to

the mother and embryo or fetus. Infants born of mothers who have received substantial doses to corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

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

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and lack of antibody response.

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

Immune System Effects
Allergic reactions may occur. 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.

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 prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure: If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

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

Ocular Effects

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

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

Metabolism and Nutrition

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

Psychiatric Effects

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

Potentially severe psychiatric adverse reactions may occur with systemic steroids. 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.

Vascular Effects

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

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 hemorrhage 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.

Caution must also be used in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer,-hypertension, when steroids are used as direct or adjunctive therapy.

Use in Children

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and use of such regimen should be restricted to the most urgent indications.

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

High doses of corticosteroids may produce pancreatitis in children.

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.

Corticosteroids should not be injected into unstable joints.

Sterile technique is necessary to prevent infections or contamination.

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

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 (Also see myopathy statement in **Musculoskeletal Effects** section).

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

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

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

Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

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.

Injury, Poisoning and Procedural Complications
Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury; a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

Other
Since complications of treatment with glucocorticoids are dependent on the amount 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 as to whether daily or intermittent therapy should be used.

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

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.

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

FERTILITY, PREGNANCY AND LACTATION
Fertility
Corticosteroids have been shown to impair fertility in animal studies (see section **PRECLINICAL SAFETY DATA**).

Pregnancy
Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. There is limited data on the use of methylprednisolone acetate in human pregnancies, and animal reproduction studies have not been done. 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. One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses.

Infants born of 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 appears to be rare in infants who were exposed *in utero* to corticosteroids.

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

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

Lactation
Corticosteroids are excreted in breast milk.

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

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme (**Table 1**).

CYP3A4 INHIBITORS – Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity (**Table 1**).

CYP3A4 INDUCERS – Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Co-administration may require an increase in methylprednisolone dosage to achieve the desired result (**Table 1**).

CYP3A4 SUBSTRATES – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with co-administration (**Table 1**).

NON-CYP3A4-MEDIATED EFFECTS – Other interactions and effects that occur with methylprednisolone are described in **Table 1** below.

Table 1. Important drug or substance interactions/effects with methylprednisolone

Drug Class or Type - DRUG or SUBSTANCE	**Interaction or Effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
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 should be monitored to maintain the desired anticoagulant effects.
Anticonvulsant - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (See section WARNINGS, Musculoskeletal, for additional information.) 2) 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.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITOR (and SUBSTRATE)
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase inhibitor - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Contraceptives (oral) - ETHINYLESTRADIOL/NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE)

Drug Class or Type - DRUG or SUBSTANCE	**Interaction or Effect**
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Immunosuppressant - CYCLOSPORINE	CYP3A4 INHIBITOR (and SUBSTRATE) 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosporine 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 co-administration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATE
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITOR (and SUBSTRATE)
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR
NSAIDs (non-steroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.
Potassium-depleting agents	When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists.

UNDESIRABLE EFFECTS

The following adverse reactions have been reported with the following contraindicated routes of administration:

Intrathecal/Epidural: Arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizure, sensory disturbance.

Table 2. Adverse Drug Reaction Table

System Organ Class (MedDRA v. 18.0)	Frequency not known (cannot be estimated from the available data)
Infections and infestations	Opportunistic infection, Infection, Peritonitis[#], Injection site infection.
Blood and lymphatic system disorders	Leukocytosis
Immune system disorders	Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction.
Endocrine disorders	Cushingoid, Hypothalamic pituitary adrenal axis suppression, Steroid withdrawal syndrome.
Metabolism and nutrition disorders	Metabolic acidosis, Sodium retention, Fluid retention, Alkalosis hypokalaemic, Dyslipidaemia, Glucose tolerance impaired, Increased requirements for insulin (or oral hypoglycemic agents in diabetics), Lipomatosis, Increased appetite (which may result in Weight increased).
Psychiatric disorders	Affective disorder (including Depressed mood, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation), Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia), Mental disorder, Personality change, Confusional state, Anxiety, Mood swings, Abnormal behavior, Insomnia, Irritability.
Nervous system disorders	Epidural lipomatosis, Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]), Seizure, Amnesia, Cognitive disorder, Dizziness, Headache.
Eye disorders	Exophthalmos, Cataract, Glaucoma, rare instances of blindness associated with intralesional therapy around the face and head, Chorioretinopathy.
Ear and labyrinth disorders	Vertigo.
Cardiac disorders	Cardiac failure congestive (in susceptible patients).
Vascular disorders	Thrombosis; Hypertension, Hypotension.
Respiratory, thoracic and Mediastinal disorders	Pulmonary embolism; Hiccups.
Gastrointestinal disorders	Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage), Intestinal perforation, Gastric haemorrhage, Pancreatitis, Oesophagitis ulcerative, Oesophagitis, Abdominal pain, Abdominal distension, Diarrhoea, Dyspepsia, Nausea.
Skin and subcutaneous tissue disorders	Angioedema, Hirsutism, Petechiae, Ecchymosis, Skin atrophy, Erythema, Hyperhidrosis, Skin striae. Rash, Pruritus, Urticaria, Acne, Skin hyperpigmentation, Skin hypopigmentation.
Musculoskeletal and connective tissue disorders	Muscular weakness, Myalgia, Myopathy, Muscle atrophy, Osteoporosis, Osteonecrosis, Pathological fracture, Neuropathic arthropathy, Arthralgia, Growth retardation.
Reproductive system and breast disorders	Menstruation irregular.
General disorders and administration site conditions	Abscess sterile, Impaired healing, Oedema peripheral, Fatigue, Malaise, Injection site reaction.
Investigations	Intraocular pressure increased, Carbohydrate tolerance decreased, Blood potassium decreased, Urine calcium increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood urea increased, Suppression of reactions to skin tests.
Injury, poisoning and procedural complications	Spinal compression fracture, Tendon rupture (particularly of the Achilles tendon).

[#] Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section WARNINGS).

Overdosage

There is no clinical syndrome of acute overdosage with DEPO-MEDROL Sterile Aqueous Suspension (methylprednisolone acetate).

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

Methylprednisolone is dialyzable.

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 disturbance and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

POSOLOGY AND METHOD OF ADMINISTRATION

Because of possible physical incompatibilities, DEPO-MEDROL Sterile Aqueous Suspension (methylprednisolone acetate) should not be diluted or mixed with other solutions. Parenteral suspensions should be inspected visually for any foreign particulate matter and discoloration prior to administration whenever drug product and container permit.

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.

General guide for dosage

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 that location where the synovial cavity is most superficial and most free of large vessels and nerves.

With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the desired amount of DEPO-MEDROL. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of the synovial fluid and the suspension. The site is covered with a small sterile dressing.

Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal, and hip joints. Since difficulty is 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 orthopedic 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 anesthetic is used prior to injection of DEPO-MEDROL, the anesthetic package insert should be read carefully and all the precautions observed.

2. Bursitis. The area around the injection site is prepared in a sterile way and a wheal at the site made with 1 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 tumor 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 30 mg. In recurrent or chronic conditions, repeated injections may be necessary.

Injections for Local Effect in Dermatologic Conditions. Following cleansing with an appropriate antiseptic, such as 70% alcohol, 20 to 60 mg 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.

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

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

Hormone therapy is 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 intramuscular injection of 40 mg every two weeks may be adequate. For maintenance of patients with rheumatoid arthritis, the weekly intramuscular dose will vary from 40 to 120 mg. The usual dosage for patients with dermatologic lesions benefitted by systemic corticoid therapy is 40 to 120 mg of methylprednisolone 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 to 120 mg. In chronic contact dermatitis, repeated injections at 5 to 10 day intervals may be necessary. In seborrheic 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 6 to 48 hours and persist for several days to two weeks.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention.

Pharmacokinetic properties

Absorption:

One in-house study of eight volunteers determined the pharmacokinetics of a single 40 mg intramuscular dose of Depo-Medrol. The average of the individual peak plasma concentrations was 14.8 ± 8.6 ng/mL, the average of the individual peak times was 7.25 ± 1.04 hours, and the average area under the curve (AUC) was 1354.2 ± 424.1 ng/mL x hours (Day 1-21).

Distribution:

Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. Its apparent volume of distribution is approximately 1.4 L/kg. The plasma protein binding of methylprednisolone in humans is approximately 77%.

Metabolism:

In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4-mediated metabolism, see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**.)

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

Elimination:

The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Total clearance is approximately 5 to 6 mL/min/kg. No dosing adjustments are necessary in renal failure.

Preclinical safety data

Based on conventional studies of safety pharmacology, repeated-dose toxicity, no unexpected hazards were identified. The toxicities seen in the repeated-dose studies are those expected to occur with continued exposure to exogenous adrenocortical steroids.

Carcinogenic potential:

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/m^2 basis.

Mutagenic potential:

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 suleptanate did not induce unscheduled DNA synthesis in primary rat hepatocytes at 5 to 1000 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.

Reproductive toxicity:
Corticosteroids have been shown to reduce fertility when administered to rats. 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.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids, such as methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), and intra-uterine growth retardation.

HOW SUPPLIED
DEPO-MEDROL Sterile Aqueous Suspension is available in the following strength and package size:

40 mg per mL - in 1 mL vial.

Store at maximum temperature 30°C

HARUS DENGAN RESEP DOKTER

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