PRODUCT MONOGRAPH

**DEPO-MEDROL®**
(methylprednisolone acetate injectable suspension USP)
20 mg/mL, 40 mg/mL, 80 mg/mL injectable suspension

Glucocorticoid

Pfizer Canada Inc.
17 300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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PRODUCT MONOGRAPH

DEPO-MEDROL®
methylprednisolone acetate injectable suspension USP

NOT FOR INTRATHecal OR INTrAvenOUS USE

Glucocorticoid

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
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<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
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<td>Intramuscular injection</td>
<td>20 mg/mL</td>
<td>Benzyl alcohol</td>
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<tr>
<td>Intra-synovial Injection</td>
<td>40 mg/mL</td>
<td>For a complete listing see Dosage Forms, Composition and Packaging section.</td>
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INDICATIONS AND CLINICAL USE

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 (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), acute and subacute bursitis, epicondylitis, acute nonspecific tenosynovitis, acute gouty arthritis, psoriatic arthritis, ankylosing spondylitis.
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, seasonal or perennial allergic rhinitis, drug hypersensitivity reactions, urticarial transfusion reactions, acute non-infectious laryngeal oedema (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**

   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.

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 in adults, 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. **Nervous System**

   Acute exacerbations of multiple sclerosis.

13. **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 AND PRECAUTIONS

   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, and Lichen Simplex chronicus (neurodermatitis), discoid lupus erythematosus, necrobiosis lipoidica diabeticorum, alopecia areata.

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

**CONTRAINDICATIONS**

DEPO-MEDROL is contraindicated:

- in patients with known hypersensitivity to any components of the product
- in patients with systemic fungal infections
- in idiopathic thrombocytopenic purpura when administered intramuscularly
- in patients administered with live or live, attenuated vaccines while receiving immunosuppressive doses of corticosteroids.
- in herpes simplex of the eye, except when used for short-term or emergency therapy as in acute sensitivity reactions
- in patients with vaccinia and varicella, except when used for short-term or emergency therapy as in acute sensitivity reactions

Depo-Medrol is not indicated for epidural and intrathecal administration. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid.
administration (see ADVERSE REACTIONS). Appropriate measures must be taken to avoid intravascular injection.

DEPO-MEDROL is contraindicated for use in premature infants because the formulation contains benzyl alcohol. See WARNINGS AND PRECAUTIONS, Special Populations; Pediatrics.

WARNINGS AND PRECAUTIONS

**Benzyl Alcohol Formulation**

20 mg/mL (5 mL vial), 40 mg/mL (2 and 5 mL vials), 80 mg/mL (5 mL vial)

Multidose use of DEPO-MEDROL (methylprednisolone acetate) 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.

Multidose use of DEPO-MEDROL from vials is not recommended for intra-synovial injection.

This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue.

DEPO-MEDROL should not be used in premature infants. The formulation contains benzyl alcohol, which has been reported to be associated with a fatal "gasping syndrome" in premature infants. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol at which toxicity may occur is not known. See also CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Pediatrics.

When multidose vials are used, special care to prevent contamination of the contents is essential. There is some evidence that benzalkonium chloride is not an adequate antiseptic for sterilizing multidose vials. A povidone-iodine solution or similar product is recommended to cleanse the vial top prior to aspiration of contents (see WARNINGS AND PRECAUTIONS).

**Myristyl Gamma Picolinium Chloride Formulation**

40 mg/mL and 80 mg/mL, (1 mL vial)

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

While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physiochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring dermal and/or subdermal changes may form depressions in the skin at the injection site. The degree to which this reaction occurs will vary with the amount of adrenal steroid injected.

Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed.
In order to 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.

**General**

DEPO-MEDROL should not be administered by any route other than those listed under INDICATIONS AND CLINICAL USE. It is critical that, during administration of DEPO-MEDROL, appropriate technique be used and care taken to assure proper route of administration.

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.

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

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual. Since complications of treatment with glucocorticoids are dependent on the 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 and as to whether daily or intermittent therapy should be used.

Caution must be used in renal insufficiency, hypertension, osteoporosis and myasthenia gravis, when steroids are used as direct or adjunctive therapy.

Serious medical events have been reported in association with the intrathecal/epidural routes of administration (see CONTRAINDICATIONS and ADVERSE REACTIONS).

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. Intra-articular injected corticosteroids may be systemically absorbed.
Carcinogenesis and Mutagenesis
Kaposi’s sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Cardiovascular
Literature reports suggest an apparent association between the use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

As sodium retention with resultant oedema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution, and only if strictly necessary, in patients with congestive heart failure. Corticosteroids should also be used with caution in hypertension, or renal insufficiency (see also WARNINGS AND PRECAUTIONS, Endocrine and Metabolism and ADVERSE REACTIONS).

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.

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.

Endocrine and Metabolism
Patients should be monitored for Hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing’s syndrome and hyperglycemia with chronic use.

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 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 re instituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

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

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

There is an enhanced effect of corticosteroids in patients with hypothyroidism. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

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

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.

**Gastrointestinal**
Corticosteroids should be used with caution in non-specific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection and in diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer, when steroids are used as direct or adjunctive therapy, since they may increase the risk of a perforation. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

Glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

**Hematologic**
Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. See also DRUG INTERACTIONS.

**Hepatic/Biliary/Pancreatic**
There is an enhanced effect of corticosteroids in patients with cirrhosis.

High doses of corticosteroids may produce acute pancreatitis.

**Immune**
Persons who are on corticosteroids are more susceptible to infections than are healthy individuals. Corticosteroids 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. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Do not use intra-articularly, intrabursally, or for intratendinous administration for local effect in the presence of acute infection.
Recent studies suggest that corticosteroids should not be used in septic shock (an unapproved indication), and suggest that increased mortality may occur in some subgroups at higher risk (e.g., elevated serum creatinine greater than 2.0 mg/dL or secondary infections).

**Fungal Infections**
Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see CONTRAINDICATIONS; DRUG INTERACTIONS).

**Special pathogens**
Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, Taxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) 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 septicemia.

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

**Tuberculosis**
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 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.

**Vaccinations**
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see CONTRAINDICATIONS. Killed or inactivated vaccines may be administered; however the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

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 in high doses, because of possible hazards of neurological complications and lack of antibody response.

**Viral Infections**
Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be
taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

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

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to increased risk of osteoporosis (e.g., postmenopausal women) before initiating corticosteroid therapy.

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

**Neurologic**
Results from one multicenter, randomized, placebo controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. Systemic corticosteroids, including DEPO-MEDROL, are not indicated for, and therefore should not be 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.

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

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

There have been reports of epidural lipomatosis in patients taking corticosteroids (including reports in children).

**Ophthalmologic**
Use of corticosteroids may produce posterior sub-capsular 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. As intraocular pressure may become elevated in some individuals, if steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored. The use of systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.
Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

**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.

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.

**Sensitivity/Resistance**
Allergic reactions may occur. Because rare instances of skin reactions and anaphylactoid reactions have occurred in patients receiving corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

**Sexual Function/Reproduction**
Steroids may increase or decrease motility and number of spermatozoa in some patients.

**Special Populations**

**Fertility**
Corticosteroids have been shown to impair fertility in animal studies (see TOXICOLOGY, Reproductive toxicity).

**Pregnant Women**
Corticosteroids readily cross the placenta. Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to human dose. Administration of corticosteroids to pregnant animals can cause fetal malformations (cleft palate, skeletal malformations) and intra-uterine growth retardation. There are no adequate and well-controlled studies in pregnant women.

Benzyl alcohol can cross the placenta.

One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids.

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

Since there is inadequate evidence of safety in human pregnancy, this drug should be used in pregnancy or by women of child bearing potential only if clearly needed and the potential benefit justifies the potential risk to the mother and embryo or fetus. Infants born to mothers who have received corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal
insufficiency. There are no known effects of corticosteroids on labour and delivery.

**Nursing Women**
Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risks to the infant.

**Pediatrics**
Benzyl alcohol, a component of this product, has been associated with serious adverse events including death, particularly in pediatric patients, including the "gasing syndrome" in neonate and low-birth weight infants. The "gasing syndrome" is characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Growth may be suppressed in children receiving long-term, daily-divided dose glucocorticoid therapy. The use of such a regimen should be restricted to those most serious indications. Pediatric patients may experience a decrease in their growth velocity at low systemic doses and in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression (e.g., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis.

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

High doses of corticosteroids may produce pancreatitis in children.

**Geriatrics**
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Monitoring and Laboratory testing**
Corticosteroids may suppress reactions to skin tests.

Dosage adjustments may be required based on the following conditions: during remission or exacerbation of the disease process; the patient’s individual response to therapy; or upon exposure of the patient to emotional or physical stress such as serious infection, surgery or injury.
Monitoring for signs and symptoms of drug-induced secondary adrenocortical insufficiency may be necessary for up to one year following cessation of long-term or high-dose corticosteroid therapy.

**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.

**ADVERSE REACTIONS**

The following adverse reactions have been reported with DEPO-MEDROL or other corticosteroids *(Frequency Not Known)*

**Allergic reactions**: Drug hypersensitivity, anaphylactic reaction, angioedema.

**Blood and lymphatic system disorders**: Leukocytosis

**Cardiovascular**: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, cardiac failure congestive (in susceptible patients), fat embolism, hypertension, hypotension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see WARNINGS AND PRECAUTIONS), pulmonary oedema, syncope, tachycardia, thromboembolism, thrombophlebitis, thrombosis, vasculitis.

**Dermatologic**: Acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, oedema peripheral, erythema, skin hyperpigmentation, skin hypopigmentation, impaired healing, rash, abscess sterile, skin striae, suppressed reactions to skin tests, skin atrophy, thinning scalp hair, urticaria, angioedema, pruritus, hyperhidrosis, injection site reaction, and injection site infection. Kaposi’s sarcoma has been reported to occur in patients receiving corticosteroid therapy.

**Endocrine**: Carbohydrate tolerance decreased, Cushingoid, moon face, weight gain, abnormal fat deposits, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin (or oral hypoglycemic agents in diabetes), glucose tolerance impaired, menstruation irregular, hypopituitarism (particularly in times of stress, as in trauma, surgery, or illness), growth retardation, steroid withdrawal syndrome, urine calcium increased, blood urea increased.

**Fluid and electrolyte disturbances**: Sodium retention, fluid retention, congestive heart failure in susceptible patients, blood potassium decreased, alkalosis hypokalemic, hypertension.

**Gastrointestinal**: Abdominal distension, abdominal pain, functional gastrointestinal disorder/bladder dysfunction, elevation in serum liver enzyme levels (usually reversible upon discontinuation), nausea, pancreatitis, peptic ulcer (with possible subsequent peptic ulcer perforation and peptic ulcer haemorrhage), intestinal perforation (particularly in patients with inflammatory bowel disease), oesophagitis ulcerative, oesophagitis, diarrhoea, dyspepsia, gastric haemorrhage.

**Hepatic**: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased. Hepatomegaly has also been observed.

**Immune System**: Infection, decreased resistance to infection, opportunistic infections, hypersensitivity reactions including anaphylaxis, suppression of reactions to skin tests, peritonitis.
**Metabolic:** Nitrogen balance negative (due to protein catabolism), dyslipidaemia, lipomatosis, increased appetite (which may result in weight gain).

**Musculoskeletal:** Osteonecrosis, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, muscle atrophy, muscular weakness, malaise, osteoporosis, pathological fracture, postinjection flare (following intra-articular use), myopathy, tendon rupture (particularly of the Achilles tendon), spinal compression fracture, arthralgia, myalgia.

**Neurologic/Psychiatric:** Convulsion, headache, intracranial pressure increased (with papilloedema [idiopathic intracranial hypertension], usually following discontinuation of treatment), vertigo, neuritis, neuropathy, paresthesia, amnesia, cognitive disorder, dizziness, epidural lipomatosis, emotional instability, insomnia, mood swings, personality change, affective disorder (including affect lability, depressed mood, euphoric mood, psychological dependence, suicidal ideation), psychotic disorder (including mania, delusion, hallucination, schizophrenia [aggravation of]), confusional state, mental disorder, anxiety, abnormal behaviour.

**Ophthalmic:** Cataract, increased intraocular pressure, glaucoma, exophthalmos, central serous chorioretinopathy.

**Reproductive System:** Increased or decreased motility and number of spermatozoa

**Other:** hiccups, fatigue, irritability, pulmonary embolism.

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

**Intrathecal/Epidural:** Arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizures, sensory disturbances.

**Intranasal:** Drug hypersensitivity, rhinitis, temporary/permanent visual impairment including blindness.

**Ophthalmic:** Intraocular pressure, infection, ocular and periocular inflammation including allergic reactions, residue or slough at injection site, temporary/permanent visual impairment including blindness.

**Miscellaneous injection sites** (*scalp, tonsillar fauces, sphenopalatine ganglion*): Blindness

**DRUG INTERACTIONS**

**Overview**

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.

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
CYP3A4 INDUCERS – Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Coadministration 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 affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration.

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

**Drug-Drug Interactions**

<table>
<thead>
<tr>
<th>Drug Class or Type - DRUG or SUBSTANCE</th>
<th>Interaction or Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterial -ISONIAZID</td>
<td>CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.</td>
</tr>
<tr>
<td>Antibiotic -RIFAMPIN</td>
<td>CYP3A4 INDUCER</td>
</tr>
<tr>
<td>Anticoagulants (oral)</td>
<td>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. Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.</td>
</tr>
<tr>
<td>Anticonvulsant - CARBAMAZEPINE</td>
<td>CYP3A4 INDUCER (and SUBSTRATE)</td>
</tr>
<tr>
<td>Anticonvulsants - PHENOBARBITAL</td>
<td>CYP3A4 INDUCERS</td>
</tr>
<tr>
<td>Anticonvulsants - PHENYTOIN</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics - NEUROMUSCULAR BLOCKERS</td>
<td>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 WARNINGS AND PRECAUTIONS - 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.</td>
</tr>
<tr>
<td>Anticholinesterases</td>
<td>Steroids may reduce the effects of anticholinesterases in myasthenia gravis. Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.</td>
</tr>
<tr>
<td>Drug Class or Type</td>
<td>Interaction or Effect</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>CYP3A4 INHIBITORS (and SUBSTRATES)</td>
</tr>
<tr>
<td>Antifungal</td>
<td>CYP3A4 INHIBITORS (and SUBSTRATE)</td>
</tr>
<tr>
<td>Antitubercular drugs</td>
<td>Serum concentrations of isoniazid may be decreased.</td>
</tr>
<tr>
<td>Antivirals</td>
<td>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.</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment. Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Cholestyramine may increase the clearance of oral corticosteroids.</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>CYP3A4 INHIBITOR (and SUBSTRATE)</td>
</tr>
<tr>
<td>Contraceptives (oral)</td>
<td>CYP3A4 INHIBITOR (and SUBSTRATE) Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
<td>Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>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 coadministration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. 3) Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with concurrent use. Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, therefore it is possible that adverse events associated with the individual use of either drug may be more apt to occur.</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>CYP3A4 SUBSTRATE</td>
</tr>
<tr>
<td>Drug Class or Type - DRUG or SUBSTANCE</td>
<td>Interaction or Effect</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.</td>
</tr>
<tr>
<td>Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN</td>
<td>CYP3A4 INHIBITOR (and SUBSTRATE) Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see PRECAUTIONS: Drug Interactions, Hepatic Enzyme Inhibitors).</td>
</tr>
<tr>
<td>Macrolide Antibacterial - TROLEANDOMYCIN</td>
<td>CYP3A4 INHIBITOR Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see PRECAUTIONS: Drug Interactions, Hepatic Enzyme Inhibitors).</td>
</tr>
<tr>
<td>NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)</td>
<td>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. 3) Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with concurrent use of corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.</td>
</tr>
<tr>
<td>Potassium-depleting agents</td>
<td>When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., diuretics Amphotericin B injection), 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. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or attenuated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see WARNINGS AND PRECAUTIONS: Immune, Vaccinations).</td>
</tr>
</tbody>
</table>

**Drug-Food Interactions**
Grapefruit juice is a CYP3A4 inhibitor. See DRUG INTERACTIONS, CYP3A4 INHIBITORS above.

**Drug-laboratory Interactions**
Corticosteroids may suppress reactions to skin tests.

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

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:

<table>
<thead>
<tr>
<th>Size of Joint</th>
<th>Examples</th>
<th>Range of Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>Knees</td>
<td>20 to 80 mg</td>
</tr>
<tr>
<td></td>
<td>Ankles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shoulders</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>Elbows</td>
<td>10 to 40 mg</td>
</tr>
<tr>
<td></td>
<td>Wrists</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>Metacarpophalangeal</td>
<td>4 to 10 mg</td>
</tr>
<tr>
<td></td>
<td>Interphalangeal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sternoclavicular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acromioclavicular</td>
<td></td>
</tr>
</tbody>
</table>

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 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 steroid 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 the 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.

4. **Injections for Local Effect in Dermatologic Conditions**

Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60 mg of the suspension is injected into the lesion.

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

When multidose vials are used, special care to prevent contamination of the contents is essential (see WARNINGS AND PRECAUTIONS; General).

B. **ADMINISTRATION FOR SYSTEMIC EFFECT**

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

Dosage must be 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 an adjunct to, and not a replacement for, conventional therapy. Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. The severity, prognosis and expected duration of the disease and the reaction of the patient to medication are primary factors in determining dosage. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper G.I. 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 benefited by systemic corticoid therapy is 40 to 120 mg DEPO-MEDROL 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.

Similarly in patients with allergic rhinitis (hay fever) an intramuscular dose of 80 to 120 mg may be followed by relief of coryzal symptoms within six hours persisting for several days to three weeks.

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

**Multiple Sclerosis**
In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of corticosteroid may be reduced only temporarily.

In the event of overdosage, no specific antidote is available.

Methylprednisolone is dialyzable.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

DEPO-MEDROL (methylprednisolone acetate) is a sterile aqueous suspension of the synthetic glucocorticoid methylprednisolone acetate. It has a strong and prolonged anti-inflammatory, immunosuppressive and anti-allergic activity. DEPO-MEDROL can be administered I.M. for a prolonged systemic activity as well as In Situ for a local treatment. The prolonged activity of DEPO-MEDROL is explained by the slow release of the active substance.

Pharmacokinetics

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 (tmax) was 7.25 ± 1.04 hours, and the average area under the curve (AUC) was 1354.2 ± 424.1 ng/mL x hrs (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 DRUG INTERACTIONS).

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 modulated by P-gp.

Excretion: 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.
STORAGE AND STABILITY

Benzyl alcohol formulation: Store at controlled room temperature (15°C to 30°C). Protect from freezing.
MGPC Formulations: Store between 20ºC to 25ºC, excursions permitted between 15ºC-30ºC. Protect from freezing.

SPECIAL HANDLING INSTRUCTIONS

See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – General.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DEPO-MEDROL (methylprednisolone acetate) is available in the following strengths containing benzyl alcohol as a preservative:
  The 20 mg/mL are supplied in 5 mL vials and packaged in cartons of 1.
  The 40 mg/mL are supplied in 2 mL and 5 mL vials and packaged in cartons of 5's.
  The 80 mg/mL are supplied in 5 mL vials and packaged in cartons of 1.

Each mL of these preparations contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone Acetate</td>
<td>20 mg</td>
<td>40 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Polyethylene Glycol 3350</td>
<td>29.5 mg</td>
<td>29.1 mg</td>
<td>28.2 mg</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>1.97 mg</td>
<td>1.94 mg</td>
<td>1.88 mg</td>
</tr>
<tr>
<td>Monobasic Sodium Phosphate</td>
<td>6.9 mg</td>
<td>6.8 mg</td>
<td>6.59 mg</td>
</tr>
<tr>
<td>Dibasic Sodium Phosphate USP</td>
<td>1.44 mg</td>
<td>1.42 mg</td>
<td>1.37 mg</td>
</tr>
<tr>
<td>Benzyl Alcohol added as preservative</td>
<td>9.3 mg</td>
<td>9.16 mg</td>
<td>8.88 mg</td>
</tr>
</tbody>
</table>

Sodium Chloride was added to adjust tonicity

DEPO-MEDROL is available in a 40 mg/mL and 80 mg/mL, 1 mL vial containing myristyl gamma picolinium chloride (MGPC).
  The 40 mg/mL are supplied in 1 mL vials and packaged in cartons of 10's.
  The 80 mg/mL are supplied in 1 mL vials and packaged in cartons of 5's.

Each mL of this preparation contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone Acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene Glycol 3350</td>
<td>29 mg</td>
<td>28 mg</td>
</tr>
<tr>
<td>Myristyl-gamma-picolinium chloride</td>
<td>0.19 mg</td>
<td>0.19 mg</td>
</tr>
</tbody>
</table>

Sodium Chloride was added to adjust tonicity
When necessary, pH was adjusted with Sodium Hydroxide and/or Hydrochloric Acid. The pH of the finished product remains within the U.S.P. specified range i.e. 3.5 to 7.0.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: methylprednisolone acetate injectable suspension USP

Chemical name: (1) Pregna-1,4-diene-3,20-dione,21-(acetyloxy)-11-17-di-hydroxy-6-methyl-, (6α,11β)-; (2) 11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione 21-acetate.

Structural Formula:

Molecular Formula: C24H32O6
Molecular Weight: 416.51
**Description:**

Methylprednisolone acetate is the 6-methyl derivative of prednisolone. It is a white or practically white, odorless, crystalline powder which melts between 205 - 208°C with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol, and slightly soluble in ether. It is practically insoluble in water. The partition coefficient is $c \log P = 1.467$

**TOXICOLOGY**

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.

**Carcinogenesis**
Long-term studies in animals have not been performed to evaluate carcinogenic potential.

**Mutagenesis**
There was no evidence of a potential for genetic and chromosome mutations when tested in limited studies performed in bacterial and mammalian cells.

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

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 induce malformations (cleft palate, skeletal malformations) and intra-uterine growth retardation.
REFERENCES


PART III: CONSUMER INFORMATION

DEPO-MEDROL
(methylprednisolone acetate injectable suspension USP)
20 mg/mL, 40 mg/mL, 80 mg/mL injectable suspension

This leaflet is part III of a three-part "Product Monograph" published when DEPO-MEDROL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DEPO-MEDROL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DEPO-MEDROL (methylprednisolone) is used in the treatment of various conditions such as allergy or inflammation.

What it does:
DEPO-MEDROL is a corticosteroid hormone (glucocorticoid). It decreases the body’s immune response to certain diseases and reduces inflammation.

When it should not be used:
Do not take DEPO-MEDROL if you have:
- allergic reaction to methylprednisolone or any other steroid medicine or any of the ingredients in DEPO-MEDROL; or
- any fungal infection or any untreated infections.
- viral diseases including vaccinia (cowpox), varicella (chicken pox), and herpes simplex of the eye.
- low platelet count.

DEPO-MEDROL should not be given to premature infants because the formulation contains benzyl alcohol.

Patients taking DEPO-MEDROL should not receive live vaccines.

What the medicinal ingredient is:
Methylprednisolone acetate

What the nonmedicinal ingredients are:
DEPO-MEDROL multi-dose with preservative benzyl alcohol, dibasic sodium phosphate, monobasic sodium phosphate, polyethylene glycol 3350 and polysorbate 80.

DEPO-MEDROL single-use: myristyl-gamma-picolinium chloride and polyethylene glycol 3350.

What dosage forms it comes in:
DEPO-MEDROL is available in the following strengths containing benzyl alcohol as a preservative:
- The 20 mg/mL are supplied in 5 mL vials and packaged in cartons of 1.
- The 40 mg/mL are supplied in 2 mL and 5 mL vials and packaged in cartons of 5’s.
- The 80 mg/mL are supplied in 5 mL vials and packaged in cartons of 1.

DEPO-MEDROL is available in a 40 mg/mL and 80 mg/mL, 1 mL vial containing myristyl gamma picolinium chloride (MGPC).
- The 40 mg/mL are supplied in 1 mL vials and packaged in cartons of 10’s.
- The 80 mg/mL are supplied in 1 mL vials and packaged in cartons of 5’s.

WARNINGS AND PRECAUTIONS

DEPO-MEDROL with preservative benzyl alcohol is not recommended for injection into the joint (intra-synovial or intra-articular injection).

Before taking DEPO-MEDROL, talk to your doctor if you have:
- an infection (such as herpes simplex, chicken pox, tuberculosis, threadworm);
- bleeding problem, blood clotting problem;
- brittle bone (osteoporosis);
- high blood pressure;
- seizures (fits);
- thyroid problem (hypothyroidism);
- muscle pain or weakness (such as myasthenia gravis);
- skin cancer (Kaposi’s sarcoma);
- heart problems such as heart failure;
- certain eye diseases such as glaucoma, cataracts; herpes infection;
- kidney disease;
- liver disease such as cirrhosis;
- certain mental or mood conditions (such as depression);
- stomach or gut problems (ulcer, ulcerative colitis);
- low potassium or calcium;
- Cushing’s disease (caused by an excess of cortisol hormone);
- weak immune response;
- high blood sugar.

Before you have any operation, tell your doctor, dentist or anesthetist that you are taking DEPO-MEDROL.

Pregnancy and breast feeding
You must tell your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant as this medicine could slow the baby’s growth.
You should also tell your doctor if you are breast feeding as small amounts of corticosteroid medicines may get into breast milk.

Children:
Corticosteroids can affect growth in children.
DEPO-MEDROL with preservative benzyl alcohol is not recommended to be used in infants since benzyl alcohol has been reported to cause “gassing syndrome” that may result in death.

INTERACTIONS WITH THIS MEDICATION

Before taking DEPO-MEDROL talk to your doctor about all your other medications, including those you bought without prescription, herbal or natural products. Especially if you are taking the following:
• drugs to treat glaucoma and epilepsy such as acetazolamide
• drugs to prevent or alleviate nausea and vomiting such as aprepitant or fosaprepitant
• drugs to treat cancer such as aminoglutethimide or cyclophosphamide
• drugs to “thin” the blood; anticoagulants such as acenocoumarol, phenindione and warfarin
• drugs to treat myasthenia gravis (a muscle condition) such as distigmine and neostigmine
• antibiotics and antifungals (such as ketoconazole, itraconazole, amphotericin B, erythromycin, clarithromycin, troleandomycin, rifampicin and rifabutin)
• aspirin and non-steroidal anti-inflammatory medicines (also called NSAIDs) such as ibuprofen
• drugs to treat epilepsy such as barbiturates, carbamazepine, phenytoin and primidone
• drugs for heartburn and acid indigestion such as cimetidine
• cyclosporine
• drugs for heart problems or high blood pressure such as calcium channel blockers, digoxin and diltiazem
• water pills (diuretics)
• hormone replacement therapy or hormonal oral contraceptives
• drugs to treat HIV infections such as indinavir or ritonavir
• pancuronium or vecuronium – or other medicines called neuromuscular blocking agents which are used in some surgical procedures
• tacrolimus – used following an organ transplant to prevent rejection of the organ
• vaccines – tell your doctor or nurse if you have recently had, or are about to have any vaccination
• drugs to treat diabetes
• drugs to treat tuberculosis
• drugs to treat high cholesterol (cholestyramine)
• aromatase inhibitors (drugs to treat breast or ovarian cancer)
• immunosuppressants (drugs that suppress or reduce the strength of the body's immune system

Do not drink grapefruit juice while taking Depo-Medrol.

Driving and Using Machines
Side effects, such as dizziness, vertigo, visual disturbance and fatigue are possible after treatment with corticosteroids. If you experience these effects, you should not drive or operate machinery.

PROPER USE OF THIS MEDICATION

DEPO-MEDROL is to be given to you as an injection to the joint (intra-articular or intra-synovial injection), or into a muscle (intramuscular injection) by your health care provider. The dose of DEPO-MEDROL is depending on your condition and how severe it is.

When your condition has improved, your dose will be reduced gradually.

DEPO-MEDROL should not be stopped abruptly.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DEPO-MEDROL can have side effects although not everybody gets them.

DEPO-MEDROL may hide symptoms of infections, may cause latent infections to become active, and may induce infections by normally inoffensive organisms due to lowered body resistance.

Potential side effects with DEPO-MEDROL include:

Allergic Reactions:
• anaphylaxis (a severe, life-threatening allergic reaction)
• cardiac arrest
• bronchospasm (narrowing of the airway)

Cardiovascular:
• heart failure
• heart attack
• arrhythmia (irregular heartbeat)
• high and low blood pressure
• blood clots
• thrombophlebitis (vein inflammation)

Dermatologic:
• thin fragile skin
• impaired wound healing
• swelling
• ecchymosis (spots caused by ruptured blood vessels)
• petechiae (reddish spot containing blood that appears in skin)
• stretch marks
• dry, scaly skin
• rash
• redness
• itching
• acne
• increased sweating
• injection site reaction
• lightening or darkening of an area of skin
• abscess
• suppressed reaction to skin tests
• thinning hair

Endocrine and Metabolism:
• development of Cushingoid state (abnormal bodily condition caused by excess corticosteroids)
• moon face (enlargement of chin and forehead)
• weight gain
• abnormal fat deposits
• suppression of pituitary-adrenal axis (a condition that could lead to disabling the body’s responses to physiological stress
such as severe infections or trauma)
- suppression of growth in children
- abnormal hair growth
- new symptoms of diabetes

Gastrointestinal:
- stomach ulcer
- stomach bleeding
- inflammation of the pancreas and esophagus
- perforation of the bowel
- nausea
- vomiting or altered sense of taste (with rapid administration of large doses)
- abdominal pain
- bloating
- diarrhea
- indigestion
- bowl/bladder dysfunction
- increased appetite

Hematology:
- Above normal white blood cell count

Hepatic:
- enlarged liver

Musculoskeletal:
- loss of muscle mass
- muscle weakness
- muscle pain
- malaise (feeling of general discomfort or uneasiness)
- osteoporosis
- pathological fractures
- vertebral compression fractures
- tendon rupture, (particularly of the Achilles tendon)
- Charcot joint disease (neuropathic arthropathy)
- pain and inflammation of the tissues surrounding the injection site
- joint pain

Neurologic:
- seizures
- headache
- vertigo
- pain and tenderness
- impaired sensation, strength, and reflexes
- sensation of tingling, tickling, prickling, or burning of a person's skin
- amnesia
- dizziness

Ophthalmologic:
- cataracts
- increased intraocular pressure
- glaucoma
- bulging of the eye
- blindness

Psychiatric:
- depression
- emotional instability
- euphoria (intense feelings of well-being, elation, happiness, excitement and joy)
- insomnia
- mood swings
- personality changes
- thoughts of suicide
- delusion
- hallucination
- confusion
- schizophrenia
- anxiety

Sexual Function/Reproduction:
- menstrual irregularities
- increased or decreased motility and number of sperm

Other:
- hiccups, fatigue, irritability

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist</th>
<th>Seek IMMEDIATE medical attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst or bleeding ulcers: symptoms of which are stomach pain, bleeding from the back passage, black or bloodstained stools and/or vomiting blood</td>
<td>Only if severe</td>
<td>√</td>
</tr>
<tr>
<td>Flare up of a previous TB* : symptoms of which could be coughing blood or pain in the chest</td>
<td>In all cases</td>
<td>√</td>
</tr>
<tr>
<td>Serious allergic reaction: symptoms of which include rash, itching/swelling (especially of the face/tongue/throat), severe dizziness and trouble breathing</td>
<td>[ ]</td>
<td>√</td>
</tr>
<tr>
<td>Signs of infection (such as persistent fever/cough/sore throat, painful urination, eye pain/discharge)</td>
<td>[ ]</td>
<td>√</td>
</tr>
<tr>
<td>High blood pressure (symptoms of which are headaches or generally feeling unwell)</td>
<td>[ ]</td>
<td>√</td>
</tr>
<tr>
<td>Fast/pounding/irregular heartbeat</td>
<td>[ ]</td>
<td>√</td>
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SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

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<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>√</td>
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<tr>
<td>Cramps and spasms</td>
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<td></td>
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<tr>
<td>Vision changes</td>
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<td></td>
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<tr>
<td>Increased thirst/urination</td>
<td>√</td>
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<tr>
<td>Mental/mood changes (such as mood swings, depression, suicidal thinking, agitation, anxiety)</td>
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<tr>
<td>Tendon pain</td>
<td>√</td>
<td></td>
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<td>Bone/joint pain</td>
<td>√</td>
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<td>Easy bruising/bleeding</td>
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<td>Pain/redness/swelling at the injection site</td>
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<td></td>
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<tr>
<td>Thinning skin</td>
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<tr>
<td>Poor wound healing</td>
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</tr>
<tr>
<td>Unusual hair growth</td>
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<td>Unusual skin growth</td>
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This is not a complete list of side effects. For any unexpected effects while taking DEPO-MEDROL, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C and 30°C. Protect from freezing. Keep out of reach and sight of children.

MGPC Formulations: Store between 20°C to 25°C, excursions permitted between 15°C-30°C. Protect from freezing.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
            Health Canada
            Postal Locator 0701D
            Ottawa, Ontario
            K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001.

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