Methylprednisolone

Medrol

4 mg and 16 mg Tablet

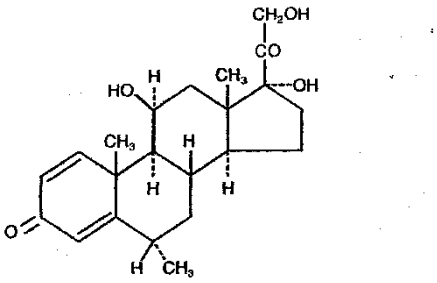
1.0 PHARMACOLOGIC CATEGORY

Corticosteroid

2.0 DESCRIPTION

Methylprednisolone (Medrol) tablet contains methylprednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water.

The chemical name for methylprednisolone is pregna-1,4-diene-3,20-dione, 11,17, 21-trihydroxy-6-methyl-,(6α, 11β)-and the molecular weight is 374.48. The structural formula is represented below:



3.0 FORMULATION

4 mg Tablet: Each tablet contains 4 mg of methylprednisolone.
16 mg Tablet: Each tablet contains 16 mg of methylprednisolone.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids, where applicable; in infancy, mineralocorticoid supplementation is of particular importance):

- Congenital adrenal hyperplasia
- Non-suppurative thyroiditis

- Hypercalcemia associated with cancer

Non-Endocrine Disorders

1. Rheumatic Disorders

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

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

2. Collagen Diseases

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

   - Systemic lupus erythematosus
   - Systemic dermatomyositis (polymyositis)
   - Acute rheumatic carditis
   - Polymyalgia rheumatica
   - Giant cell arteritis

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

4. Allergic States

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

   - Seasonal or perennial allergic rhinitis
   - Serum sickness
   - Bronchial asthma
   - Drug hypersensitivity reactions
   - Contact dermatitis
   - Atopic dermatitis

5. Ophthalmic Diseases

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

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

6. Respiratory Disease

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

7. Hematologic Disorders

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

8. Neoplastic Diseases

For palliative management of:

- Leukemias and lymphomas in adults
- Acute leukemia of childhood

9. Edematous States

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

10. Gastrointestinal Diseases

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

- Ulcerative colitis
- Regional enteritis

11. Nervous System

- Acute exacerbations of multiple sclerosis
- Management of edema associated with brain tumor

12. Organ Transplantation

13. Miscellaneous

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

4.2 Dosage and Method of Administration

The initial dosage of methylprednisolone tablets may vary depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice, while in selected patients, higher initial doses may be required. Clinical situations in which high-dose therapy may be indicated include cerebral edema

(200-1000 mg/day), organ transplantation (up to 7 mg/kg/day), and multiple sclerosis. In treatment of acute exacerbations of multiple sclerosis, oral methylprednisolone regimens of 500 mg/day for 5 days or 1000 mg/day for 3 days have been shown to be effective. If after a reasonable period of time there is a lack of satisfactory clinical response, methylprednisolone tablets should be discontinued and the patient transferred to other appropriate therapy. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage, which will maintain an adequate clinical response, is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation, it may be necessary to increase the dosage of methylprednisolone tablets for a period of time consistent with the patient's condition.

It should be emphasized that dosage requirements are variable and must be individualized on the basis of the disease under treatment and the response of the patient.

Alternate Day Therapy (ADT): Alternate day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticosteroid is administered every other morning. The purpose of this mode of therapy is to provide a patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

4.3 Contraindications

Methylprednisolone tablets are contraindicated in patients who have:

- Systemic fungal infections
- Known hypersensitivity to methylprednisolone tablets or to methylprednisolone, or any component of the tablet namely, lactose monohydrate, maize starch, corn starch, liquid paraffin, sucrose, and calcium stearate.

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

4.4 Special Warnings and Precautions for Use

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. Infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that

affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

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

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

The use of 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.

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

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended, and a systematic review concluded that short-course, high-dose corticosteroids did not support their use. However, meta-analyses and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor-dependent septic shock.

Immune System

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

Because rare instances of skin reactions and anaphylactic/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.

This medicine contains lactose produced from cow’s milk. Caution should be exercised in patients with a known or suspected hypersensitivity to cow’s milk or its components or other dairy products because it may contain trace amounts of milk ingredients.

Endocrine

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 the use of alternate-day therapy (see Section **4.2 Dosage and Method of Administration,** Alternate Day Therapy).

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

Drug-induced 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.

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.

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

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

Potentially severe psychiatric adverse reactions may occur with systemic steroids (see Section **4.8 Undesirable Effects,** Psychiatric disorders). Symptoms typically emerge

within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

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

Nervous System

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

Corticosteroids should be used with caution in patients with myasthenia gravis (see myopathy statement in Musculoskeletal Effects section).

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

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

Ocular

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

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

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

Cardiac

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. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy.

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

Vascular

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

Corticosteroids should be used with caution in patients with hypertension.

Gastrointestinal

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, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary

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

Musculoskeletal

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

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

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

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

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.

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. Alternate day glucocorticoid therapy usually avoids or minimizes this side

effect (see Section **4.2 Dosage and Method of Administration**, Alternate Day Therapy).

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

High doses of corticosteroids may produce pancreatitis in children.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A4 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 toxicity.

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.

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.

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

Table 1 provides a list and descriptions of the most common and/or clinically important drug interactions or effects with methylprednisolone.

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

Drug Class or Type - DRUG or SUBSTANCE	**Interaction/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,

Drug Class or Type **- DRUG or SUBSTANCE**	**Interaction/Effect**
	coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - 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 **4.4 Special Warnings and Precautions for Use**, 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 INHIBITORS (and SUBSTRATES)
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 inhibitors -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)
- 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 SUBSTRATES
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
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, xanthines, or beta2 agonists.

4.6 Fertility, Pregnancy and Lactation

Fertility

Corticosteroids have been shown to impair fertility in animal studies (see Section **5.3 Preclinical Safety Data**).

Pregnancy

Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women.

Since adequate human reproductive studies have not been done with methylprednisolone, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Some 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 to mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency, although neonatal adrenal insufficiency appears to be rare in infants who were exposed *in utero* to corticosteroids.

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

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

Lactation

Corticosteroids are excreted in breast milk. Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants.

This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

Table 2. Adverse Drug Reaction Table

System Organ Class (MedDRA v. 18.0)	Adverse Drug Reactions
Infections and infestations	Opportunistic infection; Infection; Peritonitis†
Blood and lymphatic system disorders	Leukocytosis
Immune system disorders	Drug hypersensitivity; Anaphylactic reaction; Anaphylactoid reaction
Endocrine disorders	Cushingoid; Hypopituitarism; Steroid withdrawal syndrome
Metabolism and nutrition disorders	Metabolic acidosis; Sodium retention; Fluid retention; Alkalosis hypokalemic; Dyslipidemia; Glucose tolerance impaired; Increased insulin requirement (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); Psychotic behavior; Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behavior; Insomnia; Irritability
Nervous system disorders	Epidural lipomatosis; Intracranial pressure increased (with Papilledema [Benign intracranial hypertension]); Seizure;Amnesia; Cognitive disorder; Dizziness; Headache
Eye disorders	Chorioretinopathy; Cataract ; Glaucoma; Exophthalmos
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 hemorrhage); Intestinal perforation; Gastric hemorrhage; Pancreatitis; Esophagitis ulcerative; Esophagitis; Abdominal distention; Abdominal pain; Diarrhea; Dyspepsia; Nausea
Skin and subcutaneous tissue disorders	Angioedema; Hirsutism; Petechia; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Skin stria; Rash; Pruritus; Urticaria; Acne
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	Impaired healing; Edema peripheral; Fatigue; Malaise

Table 2. Adverse Drug Reaction Table

System Organ Class (MedDRA v. 18.0)	Adverse Drug Reactions
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

*****Not a MedDRA PT

[†]Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see Section **4.4 Special Warnings and Precautions for Use**).

4.9 Overdose and Treatment

There is no clinical syndrome of acute overdosage with corticosteroids. 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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 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. The relative potency of methylprednisolone to hydrocortisone is at least four to one.

5.2 Pharmacokinetic Properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Absorption:

Methylprednisolone is rapidly absorbed and the maximum plasma methylprednisolone concentration is achieved around 1.5 to 2.3 hours across doses following oral administration in normal healthy adults. The absolute bioavailability of methylprednisolone in normal healthy subjects is generally high (82% to 89%) following oral administration.

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 enzyme. For a list of drug interactions based on CYP3A4-mediated metabolism, see Section **4.5 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.

5.3 Preclinical Safety Data

The non-clinical database, in combination with evidence of safety gleaned from years of clinical experience and post-marketing surveillance, supports the safety of methylprednisolone tablets as a potent anti-inflammatory agent in short-term inflammatory disorders.

Based on conventional studies of safety pharmacology, repeated-dose toxicity in mice, rats, rabbits, and dogs using intravenous, intraperitoneal, subcutaneous, intramuscular, and oral routes of administration, 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 1,000 µg/mL. Moreover, a review of published data indicates that prednisolone farnesylate (PNF), which is structurally similar to methylprednisolone, was not mutagenic with or without

metabolic activation in *Salmonella typhimurium* and *Escherichia coli* strains at 312 to 5,000 µg/plate. In a Chinese hamster fibroblast cell line, PNF produced a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested 1,500 µg/mL.

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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date of the product.

6.2 Storage Condition

Methylprednisolone (Medrol) 4 mg Tablet: Store at temperatures not exceeding 30°C.
Methylprednisolone (Medrol) 16 mg Tablet: Store at temperatures not exceeding 25°C.

6.3 Availability

Methylprednisolone (Medrol) 4 mg tablets: White elliptical tablets, cross-scored on one side and marked “UPJOHN” on the other side. Available in Blisters of 10’s (in Boxes of 100’s).

Methylprednisolone (Medrol) 16 mg tablets: White elliptical tablets, cross-scored on one side and marked “UPJOHN 73” on the other side. Available in Blisters of 10’s (in Boxes of 30’s).

7.0 FDA REGISTRATION NUMBER

Medrol 4 mg Tablet: DRP-3440
Medrol 16 mg Tablet: DRP-3441

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Medrol 4 mg Tablet: 15 April 1958
Medrol 16 mg Tablet: 04 November 1971

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
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63100 Ascoli Piceno (AP), Italy

Marketing Authorization Holder:
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Revision No.: 10.1.1
Revision Date: 12 September 2023
Reference: CDS Version 16.0, 17.0/Storage condition correction/MAH Office Address and other minor updates
Reference Date: 03 December 2018, 26 June 2019