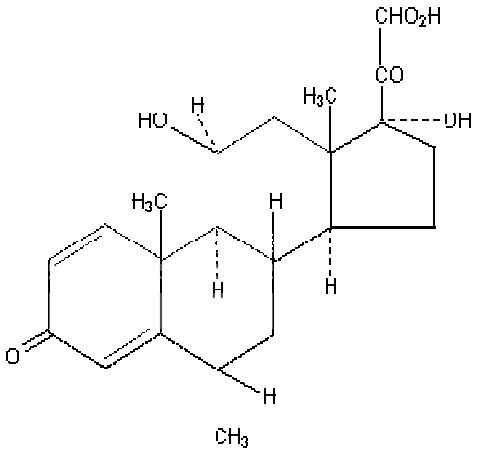
PT. PFIZER INDONESIA
Local Product Document

Generic Name: Methylprednisolone tablets
Trade Name: **MEDROL®**
CDS Effective Date: February 07, 2025
Supersedes: August 01, 2023

DESCRIPTION

MEDROL® Tablets contain methylprednisolone, which is a glucocorticoid. Glucocorticoids are adrenocortical steroids but 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:



Each MEDROL® Tablet for oral administrations contains 4 mg of methylprednisolone.

PHARMACEUTICAL FORM

Half oval, elliptical, white tablets, debossed “MEDROL 4” on one side and double scored on the other side.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

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

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 **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.

Elimination:
The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours.

Methylprednisolone clearance is altered by concurrent administration of troleandomycin, erythromycin, rifampicin, anticonvulsants and theophylline.

No dosing adjustments are necessary in renal failure.

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 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.

INDICATIONS

MEDROL® Tablets are indicated in the following conditions:

1. 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

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

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

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

5. Allergic States

Control of severe or incapacitating allergic condition intractable to adequate trials of conventional treatments:
- Seasonal or perennial allergic rhinitis
- Drug hypersensitivity reactions
- Serum sickness
- Bronchial asthma
- Contact dermatitis
- Atopic dermatitis

6. Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as:
- Allergic corneal marginal ulcers
- Herpes zoster ophthalmicus
- Anterior segment inflammation
- Diffuse posterior uveitis and choroiditis
- Sympathetic ophthalmia
- Keratitis
- Allergic conjunctivitis
- Optic neuritis
- Chorioretinitis
- Iritis and iridocyclitis

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

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

9. Neoplastic Diseases
For palliative management of:
- Leukemias and lymphomas in adults
- Acute leukemia of childhood

10. 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.

11. Gastrointestinal Diseases
To tide the patient over a critical period of the diseases in:
- Ulcerative colitis
- Regional enteritis

12. Nervous System
Acute exacerbation of multiple sclerosis.

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

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

WARNINGS

Immunosuppressant Effects/Increased Susceptibility to Infections
Corticosteroids may increase susceptibility to infection, may mask some sign of infection, exacerbate existing infections, increase the risk of reactivation or exacerbation of latent infections

and new infections may appear during their use. There may be decreased resistance and inability to localized infection when corticosteroids are used.

Monitor for the development of infection and consider withdrawal of corticosteroids or dosage reduction as needed.

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.

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

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

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation if necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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 **POSOLOGY AND METHOD OF ADMINISTRATION**.)

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 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.

Particular care is required when considering the use of systemic corticosteroids in patients with Diabetes mellitus (or a family history of diabetes) and frequent patient monitoring is necessary.

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

Potentially severe psychiatric adverse reactions may occur with systemic steroids (See section **ADVERSE REACTIONS**). 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** 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 **POSOLOGY 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 patient 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 and may enhance the establishment of secondary ocular infections due to fungi or viruses.

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 ulcer 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; 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. Cases of rhabdomyolysis have been reported. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.
Osteoporosis is a common but infrequently recognized adverse effects 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 affects 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.

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

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 doses glucocorticoid therapy and use of such regimen should be restricted to the most urgent indication. Alternate day glucocorticoid therapy usually avoids or minimizes these side effects (See section **POSOLOGY AND METHOD OF ADMINISTRATION**).

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

High doses of corticosteroids may produce pancreatitis in children.

Host defenses are impaired in patient receiving large doses of glucocorticoids and this effect increases susceptibility to fungus infection as well as bacterial and viral infections.

Fertility, Pregnancy and Lactation
Fertility
Corticosteroids have been shown to impair fertility in animal studies (See section **Preclinical safety data**).

Pregnancy
Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fatal malformations.

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 to 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.

Lactation
Corticoids are excreted in breast milk and mothers taking the drug should not be breast feed.
This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

Effects on ability to drive and use machines
The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated.

Undesirable effects, such as dizziness, vertigo, visual disturbances and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

PRECAUTIONS

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Since concurrent administration of these agents result in a mutual inhibition of metabolism, it is possible that convulsion and other adverse events associated with the individual use of either drug may be more apt to occur.

DRUG INTERACTIONS

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 - RIFABUTIN	CYP3A4 INDUCERS
Anticonvulsants - PHENOBARBITAL - PHENYTOIN - PRIMIDONE	CYP3A4 INDUCERS
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Calcium Antagonist - MIBEFRADIL	CYP3A4 INHIBITOR
Histamine H2 receptor Antagonist - CIMETIDINE	CYP3A4 INHIBITOR
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)
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITORS (and SUBSTRATES)
Contraceptives (oral) - ETHINYLESTRADIOL/NORETHINDRONE	CYP3A4 INHIBITORS (and SUBSTRATES)
Immunosuppressant - CYCLOSPORINE	CYP3A4 INHIBITORS (and SUBSTRATES) 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.

Drug Class or Type **- DRUG or SUBSTANCE**	**Interaction/Effect**
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	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.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
NSAIDs (non-steroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)	NON-CYP3A4-MEDIATED EFFECTS 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.
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (See section **WARNINGS,** Musculoskeletal, for additional information) 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
Anticoagulants (oral) -VITAMIN K ANTAGONISTS	The efficacy of coumarin vitamin K antagonists (e.g., warfarin, acenocoumarol, fluindione) may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.
Potassium-depleting agents	When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists.

ADVERSE REACTIONS

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
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, Hypothalamic pituitary adrenal axis suppression, Steroid withdrawal syndrome
Metabolism and nutrition disorders						Metabolic acidosis, Sodium retention, Fluid retention, Alkalosis hypokalaemic, Dyslipidaemia, Glucose tolerance impaired, Increased 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 behaviour, Mental disorder, Personality change, Confusional state, Anxiety, Mood swings, Abnormal behaviour, Insomnia, Irritability
Nervous system disorders						Epidural lipomatosis, Intracranial pressure increased (with Papilloedema [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, Flushing
Respiratory, thoracic and mediastinal						Pulmonary embolism, Hiccups

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
disorders						
Gastrointestinal disorders						Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage), Intestinal perforation, Gastric haemorrhage, Pancreatitis, Oesophagitis ulcerative, Oesophagitis, Abdominal distension, Abdominal pain, Diarrhoea, Dyspepsia, Nausea
Skin and subcutaneous tissue disorders						Angioedema, Hirsutism, Petechiae, Ecchymosis, Skin atrophy, Erythema, Hyperhidrosis, Skin striae, Rash, Pruritus, Urticaria, Acne, Panniculitis
Musculoskeletal and connective tissue disorders						Muscular weakness, Myalgia, Myopathy, Muscle atrophy, Rhabdomyolysis,, Osteoporosis, Osteonecrosis, Pathological fracture, Neuropathic arthropathy, Arthralgia, Growth retardation
Reproductive system and breast disorders						Menstruation irregular
General disorders and administration site conditions						Impaired healing, Oedema peripheral, Fatigue, Malaise
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 **WARNINGS**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
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Overdose
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.

POSOLOGY AND METHOD OF ADMINISTRATION

The initial dosage of MEDROL® Tablets may vary from 4 mg to 48 mg as methylprednisolone per day depending on the specific disease entity being treated. In situations less severity, lower doses will generally suffice while in selected patients higher initial doses may be required. Clinical situation in which high dose therapy may be indicated include multiple sclerosis (160 mg/day for a week followed by 64 mg every other day for 1 month have been shown to be effective). If after a reasonable period of time there is a lack of satisfactory clinical response, MEDROL® 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 decrement at appropriate time interval 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 situation which may make dosage adjustment necessary are changes in clinical status secondary to remission or exacerbation in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situation not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of MEDROL® 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 effect of corticosteroid, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

Elderly patient: Treatment of elderly patients, particularly if long-term, should be planned bearing in mind the more serious consequences of the common side effects of corticosteroid in old age, particularly osteoporosis, diabetes, hypertension, susceptibility to infection and thinning of skin.

Children: In general dosage for children should be based upon clinical response and is at the discretion of the clinician. Treatment should be limited to the minimum dosage for the shortest period of time. If possible, treatment should be administered as a single dose on alternate days.

LIST OF EXCIPIENT
Lactose monohydrate. Corn starch, Sucrose, Calcium stearate.

HOW SUPPLIED

Box of 10 blisters @ 10 tablets, Reg. No. DKI0554200510A1

Store below 30˚C

HARUS DENGAN RESEP DOKTER

Manufactured by:
Pfizer Italia S.r.l., Ascoli, Italy

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia