Methylprednisolone Tablets I.P.

MEDROL®

1. GENERIC NAME

Methylprednisolone Tablets I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains 4 mg, 8 mg or 16 mg of Methylprednisolone I.P.

List of Excipients

Medrol **4 mg**: Lactose monohydrate, Sucrose, Calcium Stearate, Corn starch

Medrol **8 mg**: Lactose monohydrate, Sucrose, Calcium Stearate, Corn Starch.

Medrol **16 mg:** Lactose monohydrate, Sucrose, Liquid Paraffin, Calcium Stearate, Corn starch.

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Dosage form: Tablets for oral administration

For strengths refer section 2.

4. 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.

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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	• acute gouty arthritis
• rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)	• post-traumatic osteoarthritis
• ankylosing spondylitis	• synovitis of osteoarthritis
• acute and subacute bursitis	• epicondylitis
• acute non-specific tenosynovitis	

2. Collagen Diseases
During an exacerbation or as maintenance therapy in selected cases of:

• systemic lupus erythematosus
• systemic dermatomyositis (polymyositis)
• acute rheumatic carditis

3. Dermatologic Diseases

• Pemphigus	• mycosis fungoides
• bullous dermatitis herpetiformis	• severe psoriasis
• severe erythema multiforme (Stevens-Johnson syndrome)	• severe seborrheic dermatitis
• exfoliative dermatitis	

4. Allergic States
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:

• seasonal or perennial allergic rhinitis	• drug hypersensitivity reactions
• serum sickness	• contact dermatitis
• bronchial asthma	• atopic dermatitis
• angioneurotic edema	• urticaria

5. Ophthalmic Diseases
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:

• allergic corneal marginal ulcers	• allergic conjunctivitis
• herpes zoster ophthalmicus	• keratitis
• anterior segment inflammation	• chorioretinitis
• diffuse posterior uveitis and choroiditis	• optic neuritis
• sympathetic ophthalmia	• iritis and iridocyclitis

6. Respiratory Disease

• symptomatic sarcoidosis	• fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
• Leoffler'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 exacerbation 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 Posology and Method of Administration

Posology

The initial dosage of Medrol (methylprednisolone) can vary from 4 to 48 mg per day depending on the severity of the disease. The initial dosage should be maintained or adjusted until a satisfactory response is not known.

If after a reasonable period of time the clinical response is not satisfactory, Medrol should be discontinued and the patient subjected to other therapy.

It must be emphasized that the dosage is variable and should be individualized on the basis of the disease treated and on the basis of patient response.

After a positive response, it is necessary to determine a maintenance dosage decreasing the initial dosage of the drug with small decreases at appropriate time intervals until reaching the lowest effective dose to maintain an adequate clinical response. The important is the check and the constant adaptation of drug dosage.

Situations that could necessitate dosage adjustments include: changes in clinical status secondary to remission or exacerbation of the disease process, individual response to the drug, effect on the patient of exposure to stressful situations not directly linked to the entity of the disease; in this last situation may be necessary to increase the dosage of medrol for a period of time compliant to the condition of the patient. If after a long-term therapy the treatment must be discontinued, is recommend a gradual decrease rather than abrupt decrease.

	Initial Dose	**Maintenance dose**
Rheumatic Disorders		
- rheumatoid arthritis		
severe	12-16 mg	6-12 mg
mildly severe	8-10 mg	4-8 mg
slight	6-8 mg	2-6 mg
teenagers	6-10 mg	2-8 mg
- disseminated lupus erythematosus	20-40 mg	8-20 mg
- Acute rheumatic fever	0.5 mg for each 450 g of body weight, until the serum mucoproteins amount to 6 mg% and the sedimentation rate remains normal for a week	
Allergic States		
- severe seasonal asthma	16-40 mg	
- severe hay fever	"	
- exfoliative dermatitis	"	
- contact dermatitis	"	

- congenital asthma	12-40 mg	4-16 mg
- intractable allergic rhinitis	"	"
- widespread atopic dermatitis	"	"
- widespread infant eczema	8-12 mg	
Inflammatory ophthalmic diseases (involving the posterior segment)		
- Acute	12-40 mg	
- Chronic	12-40 mg	2-12 mg
Miscellaneous		
- adrenogenital syndrome		4-12 mg
- ulcerative colitis	16-60 mg	
- leukemia	12-16 mg	
- nephrosis	20-60 mg (10-14 days or until diuresis appears)	12-40 mg (3 consecutive days per week for 6-12 months)

4.3 Contraindications

Methylprednisolone tablets are contraindicated in patients who have:

- Systemic fungal infections
- Known hypersensitivity to methylprednisolone tablets or to any of the excipient listed in the section 6.1.

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, exacerbate existing infections, increase the risk of reactivation or exacerbation of latent infections. New infections may appear during their use must be considered the possibility of establishing an appropriate antibiotic therapy.

During the use with corticosteroids may occur a decrease resistance and inability to localize infection when corticosteroids are used. Infections caused by any pathogen, including viral, bacterial and fungal infections, or caused by protozoa or helminths, localized in any part of 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.

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.

During treatment with corticosteroids, patients should not be vaccinated against smallpox.

Due to the possibility of the risk of neurological complications and a decrease of the antibody response do not perform other procedures of immunization in patients receiving corticosteroid therapy, especially at high doses.

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.

Effect on the 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.

Effects on the Endocrine System

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.

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.

In the course of therapy is suggested to gradually reduce the dosage in order to find the lowest maintenance dose.

Thyrotoxic Periodic Paralysis (TPP) can occur in patients with hyperthyroidism and with methylprednisolone-induced hypokalaemia.
TPP must be suspected in patients treated with methylprednisolone presenting signs or symptoms of muscle weakness, especially in patients with hyperthyroidism.
If TPP is suspected, levels of blood potassium must be immediately monitored and adequately managed to ensure the restoration of normal levels of blood potassium.

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 can be necessary. Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers can 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.

Effects on the 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 also the paragraph Musculoskeletal Effects).

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, Posology and Method of Administration).

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

Ophthalmic Diseases

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

Visual Disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids. Central serous chorioretinopathy, may lead to retinal detachment.

Cardiac and Vascular System

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.

With the use of corticosteroids, cases of thrombosis have been reported, including venous thromboembolism. Consequently, it has been reported corticosteroids should be used with caution in patients who suffer from or may be predisposed to thromboembolic disorders.

Corticosteroids should be used with caution in patients with hypertension.

Effects on the Gastrointestinal System

High doses of corticosteroids may cause 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.

Effects on the Hepatobiliary System

In patients with cirrhosis of the liver, the effect of corticosteroids is increased.

Hepatobiliary disorders have been reported which, in most cases, are reversible after discontinuation of therapy. Consequently, adequate monitoring is necessary.

Effects on the Musculoskeletal System

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) (see Nervous System Effects). 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 System Disorders

Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone.

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

Investigations

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

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects (see section 4.5).

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

Concomitant use of oral anticoagulants and methylprednisolone may increase the risk of bleeding. There are reports of diminished effects of oral anticoagulants as well. For patients treated with vitamin K antagonists, more frequent monitoring of prothrombin time (INR) is recommended, especially during treatment initiation or dose adjustments of methylprednisolone (see section 4.5).

The administration of corticosteroids may reduce or abolish the response to skin tests.

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.

Paediatric Population

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

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

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

High doses of corticosteroids may produce pancreatitis in children.

Use in the Elderly

Caution is recommended with prolonged treatment with corticosteroids in the elderly due to a potential increased risk of osteoporosis, as well as an increased risk of water retention, thus possibly resulting in hypertension.

Important information about some of the ingredients

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine may contain traces of milk protein as a lactose extraction residual.
Caution is advised in patients with known or suspected allergy to cow's milk proteins.
This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine.

4.5 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	CYP3A4 INDUCER
Oral anticoagulants (Vitamin K antagonists and non vitamin K antagonists)	The effect of the concomitant use of methylprednisolone with oral anticoagulants could vary. There are reports of enhanced as well as diminished effects of these anticoagulants when given concurrently with corticosteroids. Therefore, 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 (for additional information see section 4.4, Special Warnings and Precautions for Use). 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) HIV-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.
Pharmacokinetic enhancers - COBICISTAT	CYP3A4 inhibitor
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)

Drug Class or Type DRUG or SUBSTANCE	Interaction/Effect
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Immunosuppressant - CYCLOSPORINE	CYP3A4 INHIBITOR (and SUBSTRATE) 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon co-administration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES.
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES).
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 Use in special population

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 foetal malformations (see section 5.3, Preclinical Safety Data).

Since adequate studies on human reproduction have not been done with methylprednisolone, this medicinal product should be used during pregnancy only when strictly necessary, at the lowest possible dose and after a careful assessment of the benefit-risk ratio to the mother and foetus.

Some corticosteroids readily cross the placenta. One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids. 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.

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

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

Breast-feeding

Corticoids are excreted in breast milk. Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate studies on the use of glucocorticoids in humans are not available, this drug should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

In pregnant women and in women who are breastfeeding the medicine should be administered in cases of real necessity under the direct supervision of a doctor.

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 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.

4.8 Undesirable Effects

In the course of therapy with methylprednisolone, especially if intense and prolonged, were reported the following side effects with the following frequencies: Very common (≥ 1/10); common (≥ 1/100, <1/10), uncommon (≥ 1/1000, <1/100), rare (≥ 1/10000, <1/1000), not known (frequency cannot be estimated available data)

Infections and infestations:

Not known: Infection, opportunistic infections, peritonitis[†].

[†] Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).

Blood and lymphatic system disorders*:*

Not known: Leukocytosis

Immune system disorders:

Not known: Drug hypersensitivity (Anaphylactic reaction, Anaphylactoid reaction).

Endocrine disorders:

Not known: Cushingoid appearance, Hypopituitarism, Steroid withdrawal syndrome.

Interference with the pituitary-adrenal axis function, particularly in times of stress. Alteration of growth in the children.

Metabolism and nutrition disorders:

Not known: Metabolic acidosis, sodium retention, fluid retention, alkalosis hypokalaemic, dyslipidaemia, impaired glucose tolerance impaired, increased insulin requirement (or oral hypoglycemic agents in diabetics), lipomatosis, increased appetite (which may result in weight gain).

Psychiatric disorders*:*

Not known: Affective disorder (including low mood, euphoria, affect lability, drug dependence, suicidal ideation), psychotic disorders (including mania, delusion, hallucination, and schizophrenia), psychotic behavior, mental disorder, personality change, confusional state, anxiety, mood swings, abnormal behavior, insomnia, irritability.

Nervous system disorders:

Not known: Epidural lipomatosis, increased intracranial pressure (with Papilloedema [Benign intracranial hypertension]), seizures, amnesia, cognitive disorder, dizziness, headache.

Eye disorders:

Not known: Cataracts, exophthalmos, glaucoma, chorioretinopathy, blurred vision (see paragraph 4.4)

Ear and labyrinth disorders*:*

Not known: Vertigo.

Cardiac disorders*:*

Not known: Alterations in electrolyte balance, which in rare cases and in susceptible patients may lead to hypertension and congestive cardiac failure.

Vascular disorders*:*

Not known: Thrombotic events, hypertension, hypotension flushing

Respiratory, thoracic and mediastinal disorders:

Not known: Pulmonary embolism, hiccups.

Gastrointestinal disorders*:*

Not known: Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage) intestinal perforation, gastric haemorrhage, pancreatitis, ulcerative oesophagitis, oesophagitis, abdominal distension, abdominal pain, diarrhoea, dyspepsia.

Skin and subcutaneous tissue disorders*:*

Not known: Angioedema, hirsutism, petechiae, ecchymosis, skin atrophy, erythema, hyperhidrosis, skin striae, rash, pruritus, urticaria, acne, panniculitis.

Musculoskeletal and connective tissue disorders:

Not known: Muscular weakness, myalgia, myopathy, muscle atrophy, osteoporosis, osteonecrosis, pathological fracture, neuropathic arthropathy, arthralgia, delayed growth.

Reproductive system and breast disorders*:*

Not known: Menstruation irregular.

General disorders and administration site conditions*:*

Not known: Impaired healing, peripheral oedema, fatigue, malaise.

Hepatobiliary disorders*:*

Not known: Increased liver enzymes (increased alanine aminotransferase, increased aspartate aminotransferase)

Investigations*:*
Not known: Increased intraocular pressure, decreased carbohydrate tolerance, decreased blood potassium, increased urine calcium, increased blood alkaline phosphatase, increased blood urea, suppression of reactions to skin tests
* Not MedDRA PT

Injury, poisoning and procedural complications:

Not known: Spinal compression fracture, tendon rupture (particularly of the Achilles tendon).

Description of selected adverse reactions
A few cases of panniculitis have been reported following dose reduction or discontinuation of therapy, particularly after prolonged treatment at high doses. Panniculitis is more common in pediatric patients than in adults and, in most cases, resolves spontaneously.

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.

4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids. In case of acute overdose are possible cardiac arrhythmias and / or cardiovascular collapse.

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 PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

MEDROL contains a synthetic glucocorticoid, the methylprednisolone, which is the 6-methyl derivative of prednisolone.
Methylprednisolone is an anti-inflammatory corticosteroid. (For details please refer to section 5.2)

5.2 Pharmacodynamic Properties

Drug therapeutic category: Systemic corticosteroids not associated – Glucocorticoids

ATC Code: H02AB04

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.

The natural glucocorticoids (hydrocortisone and cortisone) also have salt and water retention properties, and are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogues are mainly used in many diseases for their potent anti-inflammatory action. The glucocorticoids induce important metabolic effects, and modify the immune responses to different stimulation.

5.3 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%.

Biotransformation:

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, Drug 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.

6. NON-CLINICAL PROPERTIES

6.1. Animal toxicology or pharmacology

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

Methylprednisolone has not been 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 carcinogenic effects occurred at doses which were less than the typical clinical doses on a mg/m^2 basis.

Mutagenesis:

Methylprednisolone has not been 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 test using Chinese hamster ovary cells at 2,000 to 10,000 µg/mL. Methylprednisolone suleptanate did not induce unexpected 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. However, 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 of 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 gelatinous secretion was observed, which may have been secondary to decreased accessory gland weight. The numbers of implantations and live foetuses were reduced

Teratogenesis:

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal reproduction studies showed that glucocorticoids such as, for example, methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations, cardiovascular defects, hydrocephalus, encefalocele, nervous system abnormalities), embryo-foetal lethality (e.g., increase in resorptions) and intra-uterine growth retardation (see section 4.6 Fertility, Pregnancy and Lactation).

7. DESCRIPTION

Methylprednisolone 4 mg Tablets are half oval, elliptical, white tablets, debossed with "MEDROL 4" on one side and double scored on the other

Methylprednisolone 8 mg Tablets are elliptical, convex, white tablets, debossed with "MEDROL 8" on one side and scored on the other Methylprednisolone 16 mg Tablets are elliptic, convex, white tablets engraved with "MEDROL 16" on one side and a cross score on the other.

8 PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

The pharmacokinetic interactions listed below are potentially clinically important. 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. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Drugs that induce hepatic enzymes such as Phenobarbital, phenytoin and rifampicin may increase the clearance of methylprednisolone and may require increase in methylprednisolone dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore the dose of methylprednisolone should be titrated to avoid steroid toxicity. Methylprednisolone may increase the clearance of chronic high dose aspirin. This could lead to a decrease in salicylic serum levels or increase the risk of salicylate toxicity when methylprednisolone is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. 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 effect.

8.2 Shelf Life

36 Months for 8 mg

60 Months for 4 mg and 16 mg

8.3 Packaging information

Medrol **4 mg**: 10 tablets packed in PVC Blister made up of PVC-Aluminium/clear PVC foil.

Medrol **8 mg**: 14 tablets packed in PVC Blister made up of PVC-Aluminium/clear PVC foil.

Medrol **16 mg**: 14 tablets packed in PVC Blister made up of PVC-Aluminium/PVC foil.

8.4 Storage and handeling instruction

Store at a temperature not exceeding 30°C.
Protect from moisture.

Instructions for Use and Handling

No specific instructions.

9. PATIENT COUNSELLING INFORMATION

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

10. DETAILS OF MANUFACTURER

Pfizer Italia S.r.L.
Località Marino del Tronto
63100 Ascoli Piceno (AP), Italy

Details of Imported & Marketed by

Pfizer Products India Private Limited
The Capital - B Wing, 1802, 18th Floor
Plot No. C-70, G Block, Bandra-Kurla Complex,
Bandra (East), Mumbai 400 051, India

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Import License no. FF-443-11085 Dated 01 July 2022* (*The license is renewed every 3 years as per regulations).

12. DATE OF REVISION

September 2026