

SUMMARY OF PRODUCT CHARACTERISTICS

SOLU-MEDROL

METHYLPREDNISOLONE SODIUM SUCCINATE

1. NAME OF THE MEDICINAL PRODUCT

SOLU-MEDROL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active *ingredient* — methylprednisolone (in the form of methylprednisolone sodium succinate)

40 mg, 125 mg, 250 mg, 500 mg, 1000 mg;

Excipients see section 6.1

3. PHARMACEUTICAL FORM

Sterile powder for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Solu-Medrol is indicated in the following conditions:

Endocrine Disorders¹

- primary or secondary adrenocortical insufficiency (in conjunction with mineralocorticoids, where applicable)
- acute adrenocortical insufficiency (mineralocorticoid supplementation may be necessary)
- shock secondary to adrenocortical insufficiency, or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present (when mineralocorticoid activity is undesirable)^{1,2}
- preoperatively, or in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful
- congenital adrenal hyperplasia
- nonsuppurative thyroiditis
- hypercalcemia associated with cancer.

Rheumatic Disorders^{1,2} (as adjunctive therapy for short-term administration in the management of an acute episode or exacerbation)

- post-traumatic osteoarthritis
- synovitis of osteoarthritis
- rheumatoid arthritis, including juvenile rheumatoid arthritis
- acute and subacute bursitis
- epicondylitis
- acute nonspecific tenosynovitis
- acute gouty arthritis
- psoriatic arthritis
- ankylosing spondylitis.

Collagen Diseases and Immune Complex Diseases (during an exacerbation or as maintenance therapy in selected cases)

- systemic lupus erythematosus (and lupus nephritis)
- acute rheumatic carditis
- systemic dermatomyositis (polymyositis)
- polyarteritis nodosa
- Goodpasture's syndrome.

Dermatologic Diseases

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

Allergic States (to control severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment)

- bronchial asthma
- contact dermatitis
- atopic dermatitis
- serum sickness
- drug hypersensitivity reactions
- urticarial transfusion reactions
- acute noninfectious laryngeal edema.

Ophthalmic Diseases (severe acute and chronic allergic and inflammatory processes involving the eye)

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

Gastrointestinal Diseases (to manage critical periods of the disease)

- ulcerative colitis
- regional enteritis.

Respiratory Diseases

- symptomatic sarcoidosis

- berylliosis
- fulminating or disseminated tuberculosis (when used concurrently with appropriate antituberculous chemotherapy)
- Loeffler's syndrome not manageable by other means
- aspiration pneumonitis
- moderate to severe *Pneumocystis jiroveci* pneumonia in AIDS patients (as adjunctive therapy when given within the first 72 hours of initial anti-pneumocystis treatment)
- exacerbations of chronic obstructive pulmonary disease (COPD).

Hematologic Disorders

- acquired (autoimmune) hemolytic anemia
- idiopathic thrombocytopenic purpura in adults
- secondary thrombocytopenia in adults
- erythroblastopenia (RBC anemia)
- congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases (palliative management)

- leukemias and lymphomas in adults
- acute leukemia of childhood
- to improve quality of life in patients with terminal cancer.

Edematous States

- To induce diuresis or remission of proteinuria in the nephrotic syndrome without uremia.

Nervous System

- cerebral edema from primary or metastatic tumors, or surgical or radiation therapy,
- acute exacerbations of multiple sclerosis
- acute spinal cord injury. The treatment should begin within 8 hours of injury.

Other Indications

- tuberculous meningitis with subarachnoid block or impending block (when used concurrently with appropriate antituberculous chemotherapy)
- trichinosis with neurologic or myocardial involvement
- organ transplantation
- prevention of nausea and vomiting associated with cancer chemotherapy.

4.2. Posology and method of administration

Solu-Medrol may be administered by intravenous (IV) injection or infusion, or by intramuscular (IM) injection. The preferred method for initial emergency use is IV injection. See Table 1 for recommended dosages. Dosage may be reduced for infants and children but should be selected based on the severity of the condition and the response of the patient rather than on the age or weight of the patient. The pediatric dosage should not be less than 0.5 mg/kg every 24 hours.

Table 1. Recommended dosages for methylprednisolone sodium succinate.

<u>Indication</u>	<u>Dosage</u>
Adjunctive therapy in life-threatening conditions	Administer 30 mg/kg IV over a period of at least 30 minutes. Dose may be repeated every 4 to 6 hours for up to 48 hours.
Rheumatic disorders unresponsive to standard therapy (or during exacerbation episodes) ⁵³	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates. 1 g/day for 1 to 4 days, or 1 g/month for 6 months.
Systemic lupus erythematosus unresponsive to standard therapy (or during exacerbation episodes) ^{54,61,62,63}	Administer 1 g/day for 3 days as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates.
Multiple sclerosis unresponsive to standard therapy (or during exacerbation episodes) ^{64,65,66,67}	Administer 500 mg/day or 1 g/day for 3 or 5 days as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates.
Edematous states, such as glomerulonephritis or lupus nephritis, unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within 1 week after therapy, or as the patient's condition dictates. 30 mg/kg every other day for 4 days, or 1 g/day for 3, 5 or 7 days.
Terminal cancer (to improve quality of life) ^{68,69}	Administer 125 mg /day IV for up to 8 weeks.
Prevention of nausea and vomiting associated with cancer chemotherapy	For mild to moderately emetogenic chemotherapy: Administer 250 mg IV over at least 5 minutes 1 hour before start of chemotherapy. Repeat dose of methylprednisolone at the initiation of chemotherapy and at the time of discharge. A chlorinated phenothiazine may also be used with the first dose of methylprednisolone for increased effect. For severely emetogenic chemotherapy: Administer 250 mg IV over at least 5 minutes with appropriate doses of metoclopramide or a butyrophenone 1 hour before start of chemotherapy. Repeat dose of

Table 1. Recommended dosages for methylprednisolone sodium succinate.

<u>Indication</u>	<u>Dosage</u>
	methylprednisolone at the initiation of chemotherapy and at the time of discharge.
Acute spinal cord injury ^{27,28}	<p>Treatment should begin within 8 hours of injury.</p> <p>For patients initiated on treatment within 3 hours of injury: Administer 30 mg/kg as an IV bolus over a 15-minute period, followed by a 45-minute pause, and then a continuous IV infusion of 5.4 mg/kg/h for 23 hours.</p> <p>For patients initiated on treatment within 3 to 8 hours of injury: Administer 30 mg/kg as an IV bolus over a 15-minute period, followed by a 45-minute pause, and then a continuous IV infusion of 5.4 mg/kg/h for 47 hours.</p> <p>There should be a separate intravenous site for the infusion pump.</p>
<i>Pneumocystis jiroveci</i> ¹⁰⁸ pneumonia in patients with AIDS ^{3,4}	<p>Therapy should begin within 72 hours of initial anti-pneumocystis treatment.</p> <p>One possible regimen is to administer 40 mg IV every 6 to 12 hours with gradual tapering over a maximum of 21 days or until the end of pneumocystis therapy.</p> <p>Due to the increased rate of reactivation of tuberculosis in AIDS patients, consideration should be given to the administration of antimycobacteria therapy if corticosteroids are used in this high risk group. The patient should also be observed for activation of other latent infections.</p>
Exacerbation of chronic obstructive pulmonary disease (COPD) ^{5,6}	<p>Two dose regimens have been studied:</p> <p>0.5 mg/kg IV every 6 hours for 72 hours, or</p> <p>125 mg IV every 6 hours for 72 hours, switch to an oral corticosteroid and taper dose. Total treatment period should be at least 2 weeks.</p>
As adjunctive therapy in other indications	Initial dose will vary from 10 to 500 mg IV, depending on the clinical condition. Larger doses may be required for short-term management of severe, acute conditions. Initial doses up to 250 mg should be administered IV over a period of at least 5 minutes, while larger doses should be administered over at least 30 minutes. Subsequent doses may be administered IV or IM at intervals dictated by the patient's response and clinical condition.

Table 1. Recommended dosages for methylprednisolone sodium succinate.

<u>Indication</u>	<u>Dosage</u>

To avoid compatibility and stability problems, it is recommended that Solu-Medrol be administered separately from other drugs whenever possible, as either IV push, through an IV medication chamber, or as an IV "piggy-back" solution (See section 6.6 **Instructions for Use/Handling**).

NOTE: Some of the Solu-Medrol formulations come with a diluent that contains benzyl alcohol (see section 4.4 Special warnings and precautions for use, Use in Children). The amount of benzyl alcohol per each <volume/unit> is xx mg.

4.3. Contraindications

Solu-Medrol is contraindicated:

- in patients who have systemic fungal infections.
- in patients with known hypersensitivity to methylprednisolone or any component of the formulation.
- for use by the intrathecal route of administration.
- for use by the epidural route of administration.
- brain damage as a result of craniocerebral injury.
- idiopathic thrombocytopenic purpura (following intramuscular administration of the medicinal product).
 - administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.
- breastfeeding.

It is not recommended to administer the medicinal product to patients with acute and subacute myocardial infarction since administration of SOLU-MEDROL in such patients may lead to the enlargement of the necrosis area, slow the formation of scar tissue and, as a result, lead to rupture of the heart muscle.

This medicinal product contains benzyl alcohol. Benzyl alcohol has been associated with "gasping syndrome" with a lethal outcome in premature infants. Administration of the medicinal product to new-born infants is not recommended.

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 or 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 appropriate anti-tuberculosis 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. A systematic review of 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 Effects

Allergic reactions 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.

The following paragraph applies only to the 20 mg and 40 mg presentations of methylprednisolone sodium succinate:

In patients receiving the 20 mg or 40 mg presentations of methylprednisolone sodium succinate during the treatment for acute allergic conditions and where these symptoms worsen or any new allergic symptoms occur, consideration should be given to the potential for hypersensitivity reactions to cow's milk ingredients (see section 4.3 Contraindications). If appropriate, administration of methylprednisolone sodium succinate should be stopped, and the patient's condition should be treated accordingly. Alternative treatments, including the use of corticosteroid formulations that do not contain ingredients produced from cow's milk, should be considered for acute allergy management, where appropriate.

Endocrine Effects

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

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

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

Drug-induced secondary adrenocortical insufficiency may therefore 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 reinstated.

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 Effects

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

Potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

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

Nervous System Effects

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

Corticosteroids should be used with caution in patients with myasthenia gravis. (Also see myopathy statement in Musculoskeletal Effects section).¹⁰²

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.

Severe medical events have been reported in association with the intrathecal/epidural routes of administration (see section 4.8 Undesirable effects).

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

Ocular Effects

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 Effects

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy.

There are reports of cardiac arrhythmias, and/or circulatory collapse, and/or cardiac arrest following the rapid administration of large intravenous doses of Solu-Medrol (more than 0.5 g administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate and may be unrelated to the speed or duration of infusion.

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

Vascular Effects

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

Steroids should be used with caution in patients with hypertension.

Gastrointestinal Effects

High doses of corticosteroids may produce acute pancreatitis.

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage may occur without significant pain.

Glucocorticoid therapy may mask peritonitis or other signs, or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

Corticosteroids should be used with caution in patients with nonspecific 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 Effects

Drug-induced liver injury such as acute hepatitis can result from cyclical pulsed IV methylprednisolone (usually at doses of 1 gm/day). The time to onset of acute hepatitis can be several weeks or longer. Resolution of the adverse event has been observed after treatment was discontinued.

Musculoskeletal Effects

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

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

Renal and urinary disorders

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

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

Investigations

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to

occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Injury, poisoning and procedural complications

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

Other

Since 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 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 nonsteroidal 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

The following statement applies only when benzyl alcohol is included in the diluent:

The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys’ capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

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.

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

High doses of corticosteroids may produce pancreatitis in children.

Hypertrophic cardiomyopathy may develop after administration of methylprednisolone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

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 6 β -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. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result.

CYP3A4 SUBSTRATES - In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected¹⁰², with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration.

NON-CYP3A4-MEDIATED EFFECTS – Other interactions and effects that occur with methylprednisolone are described in Table 2 below.

Table 2 provides a list and descriptions of the most common and/or clinically important drug interactions or effects with methylprednisolone.

Table 2. 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 ¹⁰² the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
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 Warnings and Precautions, Musculoskeletal, for additional information.) 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis. ^{94,95,96,97}
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. ^{98,99}
Aromatase inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate ¹⁰² 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 coadministration. 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 (nonsteroidal 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. ¹⁰²

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
Potassium depleting agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics) ¹⁰² 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.

Incompatibilities

To avoid compatibility and stability problems, it is recommended that Solu-Medrol be administered separately from other compounds that are administered via the IV route of administration. Drugs that are physically incompatible in solution with Solu-Medrol include but are not limited to: allopurinol sodium, doxapram hydrochloride, tigecycline, diltiazem hydrochloride calcium gluconate, vecuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol. (See section 6.2 for additional information.)

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

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 sodium succinate, 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 treated with long-term corticosteroids during pregnancy.

The following statement applies only when benzyl alcohol is included in the diluent:

Benzyl alcohol can cross the placenta. (See Section 4.4 Special warnings and precautions for use)

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 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

The following adverse reactions have been reported with the following contraindicated routes of administration: Intrathecal/Epidural: Arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizure, sensory disturbance.

Table 3. Adverse Drug Reaction Table

System Organ Class (MedDRA v. 18.0)	Adverse Drug Reactions
<i>Infections and infestations</i>	Opportunistic infection; Infection; Peritonitis [#]
<i>Blood and lymphatic system disorders</i>	Leukocytosis
<i>Immune system disorders</i>	Drug hypersensitivity; Anaphylactic reaction, Anaphylactoid reaction
<i>Endocrine disorders</i>	Cushingoid; Hypopituitarism; Steroid withdrawal syndrome
<i>Metabolism and nutrition disorders</i>	Metabolic acidosis ¹⁴ ; 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)
<i>Psychiatric disorders</i>	Affective disorder (including Depressed mood, Euphoric mood, affect lability, Drug dependence, Suicidal ideation); Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia); Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behaviour; Insomnia; Irritability
<i>Nervous system disorders</i>	Epidural lipomatosis; Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]); Seizure; Amnesia; Cognitive disorder; Dizziness; Headache
<i>Eye disorders</i>	Chorioretinopathy; Cataract; Glaucoma; Exophthalmos
<i>Ear and labyrinth disorders</i>	Vertigo

Table 3. Adverse Drug Reaction Table

System Organ Class (MedDRA v. 18.0)	Adverse Drug Reactions
<i>Cardiac disorders</i>	Cardiac failure congestive (in susceptible patients); Arrhythmia
<i>Vascular disorders</i>	Thrombosis; Hypertension; Hypotension
<i>Respiratory, thoracic and mediastinal disorders</i>	Pulmonary embolism; Hiccups
<i>Gastrointestinal disorders</i>	Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage); Intestinal perforation; Gastric haemorrhage; Pancreatitis; Oesophagitis ulcerative; Oesophagitis; Abdominal distention; Abdominal pain; Diarrhoea; Dyspepsia; Nausea
<i>Hepatobiliary disorders</i>	Hepatitis†
<i>Skin and subcutaneous tissue disorders</i>	Angioedema; Hirsutism; Petechiae; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Skin striae; Rash; Pruritus; Urticaria; Acne; Skin hypopigmentation
<i>Musculoskeletal and connective tissue disorders</i>	Muscular weakness; Myalgia; Myopathy; Muscle atrophy; Osteoporosis; Osteonecrosis; Pathological fracture; Neuropathic arthropathy; Arthralgia; Growth retardation
<i>Reproductive system and breast disorders</i>	Menstruation irregular
<i>General disorders and administration site conditions</i>	Impaired healing; Oedema peripheral; Fatigue; Malaise; Injection site reaction
<i>Investigations</i>	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*·
<i>Injury, poisoning and procedural complications</i>	Spinal compression fracture; Tendon rupture

* Not a MedDRA PT

† Hepatitis has been reported with IV administration (see section 4.4 Special warnings and precautions for use).

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

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.⁶⁰

5. 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.

Solu-Medrol has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The relative potency of Solu-Medrol and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to one. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.

5.2. Pharmacokinetic properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Absorption:

After a 40 mg intramuscular dose of Solu-Medrol to fourteen healthy adult male volunteers, the average peak concentration of 454 ng/mL was achieved at 1 hour. At 12 hours, the methylprednisolone plasma concentration has declined to 31.9 ng/mL. No methylprednisolone was detected 18 hours after dosing. Based on area-under-the-time-concentration curve, an indication of total drug absorbed, intramuscular Solu-Medrol was found to be equivalent to the same dose administered intravenously.

Results of a study demonstrated that the sodium succinate ester of methylprednisolone is rapidly and extensively converted to the active methylprednisolone moiety after all routes of administration. Extent of absorption of free methylprednisolone following IV and IM administrations were found to be equivalent and significantly greater than those following administration of the oral solution and oral methylprednisolone tablets. Since the extent of methylprednisolone absorbed following the IV and IM treatment was equivalent in spite of the greater amount of the hemisuccinate ester reaching the general circulation after IV administration, it appears that the ester is converted in the tissue after IM injection with subsequent absorption as free methylprednisolone.

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 20 α -hydroxymethylprednisolone and 20 β -hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4-

mediated metabolism, see Section 4.5 Interactions 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 data⁶⁰

Based on conventional studies of safety pharmacology and 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 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/m² basis.

Mutagenesis:

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 sulfonate 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. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

sodium dihydrophosphate monohydrate, sodium hydrophosphate.

Diluent: 9 mg benzyl alcohol, water for injections q.s. up to 1 ml.

6.2. Incompatibilities

The IV compatibility and stability of Solu-Medrol solutions and with other drugs in intravenous admixtures is dependent on admixture pH, concentration, time, temperature, and the ability of methylprednisolone to solubilize itself. Thus to avoid compatibility and stability problems, whenever possible it is recommended that Solu-Medrol be administered separately from other drugs and as either IV push, through an IV medication chamber, or as an IV “piggy-back” solution. (See section 4.5 for additional information.)

6.3. Shelf life

Solu-Medrol 40mg, 125mg - 2 years

Solu-Medrol 250mg, 500mg, 1000mg - 5 years

6.4. Special precautions for storage

Store unconstituted product at controlled room temperature 15-25°C (59°-77° F). Store Solution at temperature 15°–25° C (below 77° F). Use solution within 12 hours after mixing.

Reconstituted solution, additionally reconstituted for solution for infusion, could be stored at temperature 20°C- 25°C no more than 6 hours or at temperature 2°C- 8°C no more than 24 hours.

Use only the supplied solvent to prepare the solution.

6.5. Nature and contents of container

Solu-Medrol 40 mg Solution for injection: 1 Act-O-Vials.

Solu-Medrol 125 mg Solution for injection: 1 Act-O-Vial.

Solu-Medrol 250 mg Solution for injection: 1 Act-O-Vial.

Solu-Medrol 500 mg Powder and solvent for solution for injection: 1 vial + 1 vial.

Solu-Medrol 1000 mg Powder and solvent for solution for injection: 1 vial + 1 vial.

6.6. Special precautions for disposal and other handling

Preparation of Solutions

To prepare solutions for intravenous infusion, first reconstitute Solu-Medrol as directed. Therapy may be initiated by administering Solu-Medrol intravenously over a period of at least five minutes (eg, doses up to 250 mg) to at least 30 minutes (eg, doses of 250 mg or more). Subsequent doses may be withdrawn and administered similarly. If desired, the medication may be administered in dilute solutions by admixing the reconstituted product with Dextrose 5% in Water, Normal Saline, Dextrose 5% in 0.45% or 0.9% Sodium Chloride.

Directions for using Act-O-Vial Two-Compartment Vial

1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering center of stopper.
4. Sterilize top of stopper with a suitable germicide.

Note: Steps 1-4 must be completed before proceeding.

5. Insert needle **squarely** through center of stopper until tip is just visible.
6. Invert vial and withdraw dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

7. Marketing Authorization Holder

Pfizer H.C.P. Corporation, USA

235, East 42nd Street, New York 10017, USA

8. Manufacturer

Pfizer Manufacturing Belgium NV, Belgium

Address:

Rijksweg 12, 2870 Puurs, Belgium

9. MARKETING AUTHORISATION NUMBER(S)

500mg-16069

1000mg-16070

250mg-16071

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23-Apr-1996

Date of last renewal: 17-Oct-2016

250mg:

Date of first authorisation: 17-Feb-1997

Date of last renewal: 17-Oct-2016

11.DATE OF REVISION OF THE TEXT

03th March 2021