Package Insert is compliant with the applicable provisions stated in A.O 2016-0008

> Update(s) in the Package Insert may correspond to a specific post-approval change(s).

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METHYLPREDNISOLONE SODIUM SUCCINATE

SOLU-MEDROL®

40 mg, 125 mg, 500 mg, and 1 g Powder for Intramuscular (IM) and Intravenous (IV) Injection

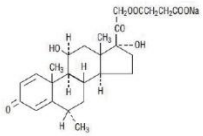
1.0 PHARMACOLOGIC CATEGORY

Corticosteroid

2.0 DESCRIPTION

This product contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate USP, occurs as a white, or nearly white, odorless hygroscopic, amorphous solid, it is very soluble in water and in alcohol. It is insoluble in chloroform and is very slightly soluble in acetone.

The chemical name for methylprednisolone sodium succinate is pregna-1, 4-diene-3, 20-dione, 21-(3-carboxy-1-oxopropoxyl-11), 17-dihydroxy-6-methyl monosodium salt, (6α, 11β).



Methylprednisolone sodium succinate is so extremely soluble in water that it may be administered in a small volume in situations in which high blood levels of methylprednisolone are required rapidly.

3.0 FORMULATION/ COMPOSITION

Methylprednisolone Sodium Succinate (Solu-Medrol) is available in several strengths and packages for intravenous or intramuscular administration.

Act-O-Vial System (Single-Dose Vial):

125 mg Powder for Injection with 2 mL diluent (DRP-2128) – Each vial approximately contains methylprednisolone sodium succinate equivalent to 125 mg of Methylprednisolone, USP. Diluent in the upper compartment of the Act-O-Vial contains Water for Injection.

40 mg Powder for Injection with 1 mL diluent (DRP-2156) – Each vial approximately contains methylprednisolone sodium succinate equivalent to 40 mg of Methylprednisolone, USP. Diluent in the upper compartment of the Act-O-Vial is Bacteriostatic Water for Injection, USP containing 0.9% w/v benzyl alcohol as preservative.

40 mg Powder for Injection with 1mL diluent (DRP-7404) – Each vial approximately contains methylprednisolone sodium succinate equivalent to 40 mg Methylprednisolone, USP. Diluent in the upper compartment of the Act-O-Vial is Water for Injection.

Vial (with diluent packaged in a separate vial):

500 mg Powder for Injection with 8 mL diluent (DRP-2157) – Each vial approximately contains methylprednisolone sodium succinate equivalent to 500 mg Methylprednisolone, USP. Diluent is Bacteriostatic Water for Injection, USP containing 0.9% w/v benzyl alcohol as preservative.

1 g Powder for Injection with 15.6 mL diluent (DRP-2155) – Each vial approximately contains methylprednisolone sodium succinate equivalent to 1 g Methylprednisolone, USP. Diluent is Bacteriostatic Water for Injection, USP containing 0.9% w/v benzyl alcohol as preservative.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Methylprednisolone sodium succinate (Solu-Medrol) is indicated in the following conditions:

Endocrine Disorders

- 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);
- 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;
- non-suppurative thyroiditis;
- hypercalcemia associated with cancer.

Rheumatic Disorders (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 non-specific 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 non-infectious 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 Dosage and Method of Administration

Methylprednisolone sodium succinate (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. 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.

Dosage requirements are variable and must be individualized on the basis of the disease under treatment, its severity and the response of the patient over the entire duration of treatment. A risk/benefit decision must be made in each individual case on an ongoing basis.

The lowest possible dose of corticosteroid should be used to control the condition under treatment for the minimum period. The proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage, which will maintain an adequate clinical response, is reached.

If after long-term therapy the drug is to be stopped, it needs to be withdrawn gradually rather than abruptly (see **Section 4.4 Special Warnings and Precautions for Use**).

Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

As adjunctive therapy in life-threatening conditions, administer 30 mg/kg IV over a period of at least 30 minutes. The dose may be repeated every 4 to 6 hours for up to 48 hours.

Methylprednisolone IV pulses, consisting of administration of 250 mg/day or above for a few days (usually ≤ 5 days) may be suitable during exacerbation episodes or conditions unresponsive to standard therapy, such as: rheumatic disorders, systemic lupus erythematosus, edematous states, such as glomerulonephritis or lupus nephritis. In multiple sclerosis unresponsive to standard therapy (or during exacerbation episodes), administer pulses of 500 or 1000 mg/day for 3 or 5 days over 30 minutes.

As adjunctive therapy in other conditions, the 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.

To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate (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 or via an infusion pump (see **Section 6.6. Special Precautions for Disposal and Other Handling**).

NOTE: Some of the methylprednisolone sodium succinate formulations come with a diluent that contains 0.9% w/v benzyl alcohol as preservative (see **Section 4.4. Special Warnings and Precautions for Use, Use in Children**).

4.3 Contraindications

Methylprednisolone sodium succinate is contraindicated:

- in patients who have systemic fungal infections.
- in patients with known hypersensitivity to methylprednisolone or any component of the formulation (see **Section 6.1. List of Excipients**).
- Methylprednisolone sodium succinate (Solu-Medrol) 40 mg Powder for Injection includes lactose monohydrate produced from cow's milk. It is therefore contraindicated in patients with a known or suspected hypersensitivity to cow's milk or its components or other dairy products because it may contain trace amounts of milk ingredients.
- for use by the intrathecal route of administration.
- for use by the epidural route of administration.

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

4.4 Special Warnings and Precautions for Use

Immunosuppressant Effects/Increased Susceptibility to Infections
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular 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.

NOTE: The following paragraph applies only to 40 mg presentation of methylprednisolone sodium succinate that include lactose monohydrate.

In patients receiving the 40 mg presentation 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 reinstituted.

A steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

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

There is an enhanced effect of corticosteroids on patients with hypothyroidism.

Metabolism and Nutrition
Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

Psychiatric 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**).

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 methylprednisolone sodium succinate (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 non-specific ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary 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 (e.g., myasthenia

gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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

Renal and Urinary 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 methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate 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 non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids.

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

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

tumor burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

Use in Children
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 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS - Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity.

CYP3A4 INDUCERS - Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Co-administration may require an increase in methylprednisolone dosage to achieve the desired result.

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

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

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

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

Drug Class or Type - DRUG or SUBSTANCE	**Interaction/Effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (see **Section 4.4. Special Warnings and Precautions for Use, Musculoskeletal Effects,** for additional information). 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)

Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE)
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Immunosuppressant - CYCLOSPORINE	CYP3A4 INHIBITOR (and SUBSTRATE) 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon co-administration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
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 beta$_2$ agonists.

Incompatibilities
To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate be administered separately from other compounds that are administered via the IV route of administration. Drugs that are physically incompatible in solution with methylprednisolone sodium succinate 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 6.5. Incompatibilities** 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 2. Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reactions
Infections and infestations	Opportunistic infection; Infection; Peritonitis[#]
Blood and lymphatic system disorders	Leukocytosis
Immune system disorders	Drug hypersensitivity; Anaphylactic reaction; Anaphylactoid reaction
Endocrine disorders	Cushingoid; Hypothalamic pituitary adrenal axis suppression; Steroid withdrawal syndrome
Metabolism and nutrition disorders	Metabolic acidosis; Sodium retention; Fluid retention; Alkalosis hypokalemic; Dyslipidemia; Glucose tolerance impaired; Increased insulin requirement (or oral hypoglycemic agents in diabetics); Lipomatosis, Increased appetite (which may result in Weight increased)
Psychiatric disorders	Affective disorder (including Depressed mood, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation); Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia); Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behavior; Insomnia; Irritability
Nervous system disorders	Epidural lipomatosis; Intracranial pressure increased (with Papilledema [Benign intracranial hypertension]); Seizure; Amnesia; Cognitive disorder; Dizziness; Headache
Eye disorders	Chorioretinopathy; Cataract; Glaucoma; Exophthalmos

Ear and labyrinth disorders	Vertigo
Cardiac disorders	Cardiac failure congestive (in susceptible patients); Arrhythmia
Vascular disorders	Thrombosis; Hypertension; Hypotension; Flushing
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism; Hiccups
Gastrointestinal disorders	Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer hemorrhage); Intestinal perforation; Gastric hemorrhage; Pancreatitis; Esophagitis ulcerative; Esophagitis; Abdominal distention; Abdominal pain; Diarrhea; Dyspepsia; Nausea
Hepatobiliary disorders	Hepatitis[†]
Skin and subcutaneous tissue disorders	Angioedema; Hirsutism; Petechiae; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Skin striae; Rash; Pruritus; Urticaria; Acne; Skin hypopigmentation
Musculoskeletal and connective tissue disorders	Muscular weakness; Myalgia; Myopathy; Muscle atrophy; Osteoporosis; Osteonecrosis; Pathological fracture; Neuropathic arthropathy; Arthralgia; Growth retardation
Reproductive system and breast disorders	Menstruation irregular
General disorders and administration site conditions	Impaired healing; Edema peripheral; Fatigue; Malaise; Injection site reaction
Investigations	Intraocular pressure increased; Carbohydrate tolerance decreased; Blood potassium decreased; Urine calcium increased; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood alkaline phosphatase increased; Blood urea increased; Suppression of reactions to skin tests*
Injury, poisoning and procedural complications	Spinal compression fracture; Tendon rupture

* Not a MedDRA PT.
[†] 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 and Treatment

There is no clinical syndrome of acute overdosage with corticosteroids.

Reports of acute toxicity and/or death following overdosage of corticosteroids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

Methylprednisolone is dialyzable.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention.

Methylprednisolone sodium succinate 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 methylprednisolone sodium succinate 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.

Methylprednisolone sodium succinate has been investigated for acute spinal cord injury in two randomized, double-blind, comparative National Acute Spinal Cord Injury Studies (NASCIS 2 and 3). The effect of high dose methylprednisolone sodium succinate given as initial bolus of 30 mg/kg by IV for 15 minutes followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hour for 24 hours was significant on neurologic recovery when given to patients within 8 hours from injury (NASCIS 2) and motor recovery was higher for those patients initiated within 3 to 8 hours from injury and treated with the same regimen for 48 hours (NASCIS 3).

5.2 Pharmacokinetic Properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Absorption
After a 40 mg intramuscular dose of methylprednisolone sodium succinate 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 methylprednisolone sodium succinate 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 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4-mediated metabolism, see **Section 4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**).

Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.

Elimination
The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Total clearance is approximately 5 to 6 mL/min/kg.

5.3 Preclinical Safety Data

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/m^2 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 suleptanate did not induce unscheduled DNA synthesis in primary rat hepatocytes at 5 to 1,000 µg/mL. Moreover, a review of published data indicates that prednisolone farnesylate (PNF), which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* and *Escherichia coli* strains at 312 to 5,000 µg/plate. In a Chinese hamster fibroblast cell line, PNF produced a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested 1,500 µg/mL.

Reproductive Toxicity
Corticosteroids have been shown to reduce fertility when administered to rats. Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have

been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids such as methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), and intra-uterine growth retardation.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

40 mg Powder for Injection (in Act-O-Vial) (DRP-2156)
Drug Product
Monobasic Sodium Phosphate, Monohydrate
Dibasic Sodium Phosphate, Dried
Lactose
Sodium Hydroxide
Water for Injection

Diluent
Benzyl alcohol
Water for Injection

40 mg Powder for Injection (in Act-O-Vial) Preservative-Free (DRP-7404)
Drug Product
Monobasic Sodium Phosphate, Anhydrous
Dibasic Sodium Phosphate, Dried
Lactose
Sodium Hydroxide
Water for Injection

Diluent
Water for Injection

125 mg Powder for Injection (in Act-O-Vial) (DRP-2128)
Drug product
Monobasic Sodium Phosphate, Anhydrous
Dibasic Sodium Phosphate, Dried
Sodium Hydroxide
Water for Injection

Diluent
Water for Injection

500 mg Powder for Injection (DRP-2157)
Drug Product
Monobasic Sodium Phosphate, Anhydrous
Dibasic Sodium Phosphate, Dried

Sodium Hydroxide
Water for Injection

Diluent
Benzyl alcohol
Water for Injection

1 g Powder for Injection (DRP-2155)
Drug Product
Monobasic Sodium Phosphate, Monohydrate
Dibasic Sodium Phosphate, Dried
Sodium Hydroxide
Water for Injection

Diluent
Benzyl alcohol
Water for Injection

6.2 Shelf-Life

See outer package for the expiry date of the product.

6.3 Storage Conditions

Methylprednisolone Sodium Succinate (Solu-Medrol) 500 mg (DRP-2157) and 1 g powder for injection (DRP-2155): Store at controlled room temperature 15°C-30°C.

Methylprednisolone Sodium Succinate (Solu-Medrol) 125 mg powder for injection (DRP-2128): Store at temperatures not exceeding 25°C.

Methylprednisolone Sodium Succinate (Solu-Medrol) 40 mg powder for injection (DRP-2156): Store at temperatures not exceeding 30°C.

Methylprednisolone Sodium Succinate (Solu-Medrol) 40 mg powder for Injection (DRP-7404): Store at temperatures not exceeding 30°C. Use within 12 hours of reconstitution if stored at 20-25°C or within 48 hours of reconstitution if stored at 2-8°C.

6.4 Availability

Methylprednisolone sodium succinate (Solu-Medrol) 40 mg Powder for Injection: Box contains 1 Act-O-Vial, with diluent in upper compartment. (DRP-2156 & DRP-7404)

Methylprednisolone sodium succinate (Solu-Medrol) 125 mg Powder for Injection: Box contains 1 Act-O-Vial, with diluent in upper compartment. (DRP-2128)

Methylprednisolone sodium succinate (Solu-Medrol) 500 mg Powder for Injection: Box contains drug vial with 8 mL diluent in a separate vial. (DRP-2157)

Methylprednisolone sodium succinate (Solu-Medrol) 1 g Powder for Injection: Box contains drug vial with 15.6 mL diluent in a separate vial. (DRP-2155)

6.5 Incompatibilities

The IV compatibility and stability of methylprednisolone sodium succinate 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 methylprednisolone sodium succinate 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. Interaction with Other Medicinal Products and Other Forms of Interaction - Incompatibilities**).

6.6 Special Precautions for Disposal and Other Handling

Preparation of Solutions
To prepare solutions for intravenous infusion, first reconstitute methylprednisolone sodium succinate as directed. Therapy may be initiated by administering methylprednisolone sodium succinate intravenously over a period of at least five minutes (e.g., doses up to 250 mg) to at least 30 minutes (e.g., 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. Dilute and use resulting solution within 12 hours following reconstitution if stored below 25°C or within 48 hours of reconstitution if stored at 2°C to 8°C.

Directions for using the 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.

7.0 FDA REGISTRATION NUMBER

40 mg Powder for Injection:	DRP-2156
40 mg Powder for Injection (Preservative-Free):	DRP-7404
125 mg Powder for Injection:	DRP-2128
500 mg Powder for Injection:	DRP-2157
1 g Powder for Injection:	DRP-2155

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

40 mg Powder for Injection:	05 Oct 2009
40 mg Powder for Injection (Preservative-Free):	18 Oct 2017
125 mg Powder for Injection:	26 Aug 1971
500 mg Powder for Injection:	28 Feb 1974
1 g Powder for Injection:	06 Sep 1974

Keep out of reach of children.

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

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

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

40 mg Powder for Injection (in Act-O-Vial)
Manufactured by:
Pfizer Manufacturing Belgium NV,
Rijksweg 12, 2870 Puurs, Belgium

40 mg Lyophilized Powder for Injection (in Act-O-Vial) Preservative-Free
Manufactured by:
Pharmacia & Upjohn Company LLC
7000 Portage Road, Kalamazoo, Michigan (MI) 49001,
United States (USA)

125 mg Powder for Injection (in Act-O-Vial)
Manufactured by:
Pharmacia & Upjohn Company LLC
7000 Portage Road, Kalamazoo, Michigan (MI) 49001,
United States (USA)

500 mg Powder for Injection
Manufactured by:
Pharmacia & Upjohn Company LLC
7000 Portage Road, Kalamazoo, Michigan (MI) 49001,
United States (USA)

Repacked by:
Hizon Laboratories, Inc.,
Assumption Rd.,
Sumulong Highway, Antipolo City

1 g Powder for Injection
Manufactured by:
Pfizer Manufacturing Belgium NV,
Rijksweg 12, 2870 Puurs, Belgium

Marketing Authorization Holder:
PFIZER, INC.
18F-20F, 8 Rockwell Building, Hidalgo Drive,
Rockwell Center, Makati City,
Metro Manila, Philippines

Under the Authority of PFIZER INC., New York, N.Y., U.S.A.

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