1.0 THERAPEUTIC CATEGORY

Corticosteroid

2.0 DESCRIPTION

Solu-Medrol Sterile Powder contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate USP, occurs as a white, or nearly white, odourless 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 prena-1,4-diene-3, 20-dione, 21-(3-carboxy-1-oxopropoxyl-11, 17-dihydroxy-6-methyl monosodium salt, (6α, 11β)

![Chemical Structure](image)

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

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/2 ml vial – Each vial approximately contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone, 2 mg anhydrous monobasic sodium phosphate, 20 mg dried dibasic sodium phosphate, and sufficient quantity of sodium hydroxide, and water for injection. Each mL of the diluent approximately contains 9 mg benzyl alcohol and sufficient quantity of water for injection.

40 mg/ml vial – Each vial approximately contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone, 2 mg monobasic sodium phosphate monohydrate, 18 mg dried dibasic sodium phosphate, 25 mg lactose, and sufficient quantity of sodium hydroxide and water for injection. Each mL of the diluent approximately contains 9 mg benzyl alcohol and sufficient quantity of water for injection.

Vial:

500 mg vial with 8 ml vial diluent – Each vial approximately contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone, 7 mg monobasic sodium phosphate, 80 mg dibasic sodium phosphate, and sufficient quantity of 10% sodium hydroxide solution, and water for injection. Each mL of the diluent approximately contains 9 mg benzyl alcohol and sufficient quantity of water for injection.
1 gram vial with 15.6 ml vial diluent – Each vial approximately contains methylprednisolone sodium succinate equivalent to 1 gram methylprednisolone, 15 mg monobasic sodium phosphate monohydrate, 140 mg dried dibasic sodium phosphate, and sufficient quantity of 10% sodium hydroxide solution, and water for injection. Each ml of the diluent approximately contains 9 mg benzyl alcohol and sufficient quantity of water for injection.

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
- nonsuppurative 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 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
- seasonal or perennial allergic rhinitis
- 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 carinii* 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, 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. 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 (Solu-Medrol).**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunctive therapy in life-threatening conditions</td>
<td>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.</td>
</tr>
</tbody>
</table>
| Rheumatic disorders 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 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. |
<p>| Systemic lupus erythematosus unresponsive to standard therapy (or during exacerbation episodes) | 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) | Administer 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 | 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. |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation episodes)</td>
<td>30 mg/kg every other day for 4 days, <strong>or</strong> 1 g/day for 3, 5 or 7 days.</td>
</tr>
<tr>
<td>Terminal cancer (to improve quality of life)</td>
<td>Administer 125 mg /day IV for up to 8 weeks.</td>
</tr>
</tbody>
</table>
| 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 methylprednisolone at the initiation of chemotherapy and at the time of discharge. |
| Acute spinal cord injury                                                  | **Treatment should begin within 8 hours of injury.**  
  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.  
  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.  
  There should be a separate intravenous site for the infusion pump. |
| Pneumocystis carinii pneumonia in patients with AIDS                      | **Therapy should begin within 72 hours of initial anti-Pneumocystis treatment.**  
  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.  
  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. |
| Exacerbation of chronic obstructive pulmonary disease (COPD)             | Two dose regimens have been studied:  
  0.5 mg/kg IV every 6 hours for 72 hours, **or**  
  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. |
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.

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 (See section 6.4 Instructions for Use/Handling).

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
- For use by the intrathecal 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.

Similarly, corticosteroids should be used with great care in patients with known or suspected parasitic infections such as *Strongyloides* (threadworm) infestation, which may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

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.

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.

**Blood and Lymphatic System**

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

**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.

**Endocrine Effects**

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. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

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

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.

**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.

**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.

**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 below.)
**Vascular Effects**
Steroids should be used with caution in patients with hypertension.

**Gastrointestinal Effects**
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.

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**
High doses of corticosteroids may produce acute pancreatitis.

**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**
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**
Methylprednisolone sodium succinate should not be used routinely to treat head injury as demonstrated by the results of a multicenter study. The study results revealed an increased mortality in the 2 weeks, or 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 Adverse Events**
Caution is recommended with prolonged corticosteroid treatment in the elderly due to a potential increase risk for osteoporosis, as well as increased risk for fluid retention with possible resultant hypertension.

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.
Use in Children
This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

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.

4.5 Interactions with Other Medicaments 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. 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 inhibited or induced, 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>
<thead>
<tr>
<th>Drug Class or Type - DRUG or SUBSTANCE</th>
<th>Interaction/Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterial - ISONIAZID</td>
<td>CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone on the acetylation rate and clearance of isoniazid.</td>
</tr>
<tr>
<td>Antibiotic, Antitubercular - RIFAMPIN</td>
<td>CYP3A4 INDUCER</td>
</tr>
<tr>
<td>Anticoagulants (oral)</td>
<td>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.</td>
</tr>
<tr>
<td>Drug Class or Type - DRUG or SUBSTANCE</td>
<td>Interaction/Effect</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>- CARBAMAZEPINE</td>
<td>CYP3A4 INDUCER (and SUBSTRATE)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>- PHENOBARBITAL</td>
<td>CYP3A4 INDUCERS</td>
</tr>
<tr>
<td>- PHENYTOIN</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (See section 4.4 Special Warnings and Precautions for Use, Musculoskeletal, for additional information.) 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.</td>
</tr>
<tr>
<td>Antiemetic</td>
<td></td>
</tr>
<tr>
<td>- APREPTITANT</td>
<td>CYP3A4 INHIBITORS (and SUBSTRATES)</td>
</tr>
<tr>
<td>- FOSAPREPTITANT</td>
<td></td>
</tr>
<tr>
<td>Antifungal</td>
<td></td>
</tr>
<tr>
<td>- ITRACONAZOLE</td>
<td>CYP3A4 INHIBITORS (and SUBSTRATES)</td>
</tr>
<tr>
<td>- KETOCONAZOLE</td>
<td></td>
</tr>
<tr>
<td>Antivirals</td>
<td>Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.</td>
</tr>
<tr>
<td>- HIV-PROTEASE INHIBITORS</td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Aminoglutethimide-induced adrenal suppression may impede endocrine changes caused by prolonged glucocorticoid treatment.</td>
</tr>
<tr>
<td>- AMINOGLUTETHIMIDE</td>
<td></td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>CYP3A4 INHIBITOR (and SUBSTRATE)</td>
</tr>
<tr>
<td>- DILTIAZEM</td>
<td></td>
</tr>
<tr>
<td>Contraceptives (oral)</td>
<td>CYP3A4 INHIBITOR (and SUBSTRATE)</td>
</tr>
<tr>
<td>- ETHINYLESTRADIOL/ NORETHINDRONE</td>
<td></td>
</tr>
<tr>
<td>- GRAPEFRUIT JUICE</td>
<td>CYP3A4 INHIBITOR</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td></td>
</tr>
<tr>
<td>- CYCLOSPORINE</td>
<td>CYP3A4 INHIBITOR (and SUBSTRATE) 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosprine 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.</td>
</tr>
<tr>
<td>- CYCLOPHOSPHAMIDE</td>
<td>CYP3A4 SUBSTRATES</td>
</tr>
<tr>
<td>- TACROLIMUS</td>
<td></td>
</tr>
<tr>
<td>NSAIDs (nonsteroidal anti-inflammatory drugs)</td>
<td></td>
</tr>
<tr>
<td>- high-dose ASPIRIN (acetylsalicylic acid)</td>
<td>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. This decrease in salicylate serum levels could lead to an increased risk of salicylate toxicity when methylprednisolone is withdrawn.</td>
</tr>
<tr>
<td>Potassium depleting agents</td>
<td>When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics, amphotericin B), patients should be</td>
</tr>
<tr>
<td>Drug Class or Type - DRUG or SUBSTANCE</td>
<td>Interaction/Effect</td>
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<tr>
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<tr>
<td></td>
<td>observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists.</td>
</tr>
</tbody>
</table>

**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, allopurinol sodium, doxapram hydrochloride, tigecycline, diltiazem hydrochloride 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 6.4 Instructions for Use/Handling for additional information.)

4.6 **Fertility, Pregnancy and Lactation**

**Fertility**

There is no evidence that corticosteroids impair fertility.

**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. Nevertheless, because the studies in humans cannot rule out the possibility of harm, methylprednisolone sodium succinate should be used during pregnancy only if clearly needed.

Some corticosteroids readily cross the placenta. One retrospective study found an increased incidence of low-birth weights in infants born of mothers receiving corticosteroids. Although neonatal adrenal insufficiency appears to be rare in infants who were exposed in utero to corticosteroids, those exposed to substantial doses of corticosteroids must be carefully observed and evaluated for signs of adrenal insufficiency.

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.

**Lactation**

Corticosteroids, including prednisolone, are excreted in breast milk.

Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risks to the infant.

The use of this drug in pregnancy, nursing mothers, or women of childbearing potential requires that the benefits of the drug be weighed against the potential risk to the mother and embryo or fetus.

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

**Infections and Infestations:** Infection, Opportunistic infections

**Immune System Disorders:** Drug hypersensitivity reactions (including Anaphylactoid or Anaphylactic reaction with or without Circulatory collapse, Cardiac arrest, Bronchospasm)

**Endocrine Disorders:** Cushingoid Hypopituitarism, Steroid withdrawal syndrome

**Metabolism and Nutrition Disorders:** Glucose tolerance impaired, Alkalosis hypokalemic, Dyslipidemia, Increased requirements for insulin (or oral hypoglycemic agents in diabetics). Sodium retention, Fluid retention, Nitrogen balance negative (due to protein catabolism), Blood urea increased, Increased appetite (which may results in Weight increased), Lipomatosis

**Psychiatric Disorders:** Affective disorder (including Affect lability, Depressed mood, Euphoric mood, psychological dependence, Suicidal ideation), Psychotic disorder (including Mania, Delusion, Hallucination, Schizophrenia [aggravation of]), Confusional state, Mental disorder, Anxiety, Personality change, Mood swings, Abnormal behaviour, Insomnia, Irritability

**Nervous System Disorders:** Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]), Convulsion, Amnesia, Cognitive disorder, Dizziness, Headache

**Eye Disorders:** Exophthalmos, Galucoma, Cataract

**Ear and labyrinth Disorders:** Vertigo

**Cardiac Disorders:** Cardiac failure congestive (in susceptible patients), Arrhythmia

**Vascular Disorders:** Hypertension, Hypotension

**Respiratory, Thoracic and Mediastinal Disorders:** Hiccups

**Gastrointestinal Disorders:** Gastric hemorrhage, Intestinal perforation, Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage), Pancreatitis, Peritonitis, Oesophagitis ulcerative, Oesophagitis, Abdominal pain, Abdominal distension, Diarrhoea, Dyspepsia, Nausea

**Skin and Subcutaneous Tissue Disorders:** Angioedema, Oedema peripheral, Ecchymosis, Petechiae, Skin atrophy, Skin striae, Skin hypopigmentation, Hirsutism, Rash, Erythema, Pruritus, Urticaria, Acne, Hyperhidrosis

**Musculoskeletal and Connective Tissue Disorders:** Osteonecrosis, Pathological fracture, Growth retardation (in children), Muscle atrophy, Myopathy, Osteoporosis, Neuropathic arthropathy, Arthralgia, Myalgia, Muscular weakness

**Reproductive System and Breast Disorders:** Menstruation irregular

**General Disorders and Administration Site Conditions:** Impaired healing, Injection site reaction, Fatigue, Malaise

**Investigations:** Alanine aminotransaminase increased, Aspartate aminotransaminase increased, Blood alkaline phosphatise increased, Intraocular pressure increased, Carbohydrate tolerance decreased. Blood potassium decreased. Urine calcium increased, suppression of reactions to skin tests.
Injury, Poisoning and Procedural Complications: r (particularly of the Achilles tendon), Spinal compression fracture

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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone and even 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.

5.2 Pharmacokinetic Properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Methylprednisolone plasma concentrations were measured by an HPLC assay. 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.

Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. The plasma protein binding of methylprednisolone in humans is approximately 77%.

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 Interactions with Other Medicinal Products and Other Forms of Interaction)
The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Its apparent volume of distribution is approximately 1.4 mL/kg and its total clearance is approximately 5 to 6 mL/min/kg.

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.

No dosing adjustments are necessary in renal failure. Methylprednisolone is hemodialyzable.

5.3 Preclinical Safety Data

Based on conventional studies of safety pharmacology, repeated-dose toxicity in mice, rats, rabbits, and dogs using intravenous, intraperitoneal, subcutaneous, intramuscular, and oral routes of administration, no unexpected hazards were identified. Methylprednisolone is a potent steroid, with pharmacological activity consistent with that of glucocorticoids, including effects on carbohydrate metabolism, electrolyte and water balance, formed elements of the blood, lymphoid tissue, and protein metabolism leading to decreased or lack of body weight gain, lymphopenia, atrophy of spleen, thymus, lymph nodes, adrenal cortex and testes, as well as fatty changes of the liver and enlargement of pancreatic islet cells. A 30-day reversibility study conducted with methylprednisolone-treated rats indicated that within approximately 1 month of drug withdrawal, normal organ function was resumed. Many parameters returned to normal after a 9-week reversibility period following 52 weeks of treatment of methylprednisolone suleptanate in rats. The toxicities seen in the repeated-dose studies are those expected to occur with continued exposure to exogenous adrenocortical steroids.

Carcinogenic potential
Long-term studies in animals have not been performed to evaluate carcinogenic potential, as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity. There is no evidence that corticosteroids are carcinogenic.

Mutagenic potential
There was no evidence of a potential for genetic and chromosome mutations when tested in a DNA damage/alkaline elution assay in Chinese hamster V-79 cells. Methylprednisolone did not induce chromosomal damage in the absence of a liver activation system.

Reproductive toxicity
In animal studies for embryotoxic effects of methylprednisolone, no teratogenic effect was observed in mice or rats at daily intraperitoneal doses of 125 mg/kg/day or 100 mg/kg/day, respectively. In rats, methylprednisolone was teratogenic when administered subcutaneously at a dose of 20 mg/kg/day. Methylprednisolone aceponate was teratogenic when given subcutaneously to rats at a dose of 1.0 mg/kg/day.

6.0 PHARMACEUTICAL PARTICULARS

6.1 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)
6.2 Shelf Life

See outer package for the expiry date of the product.

6.3 Special Precautions for Storage


6.4 Instructions for Use/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 (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; the resulting solutions are physically and chemically stable for 48 hours.

Directions for using the Act-O-Vial System

1. Press down on plastic activator to force diluent into the lower compartment.

2. Gently agitate to effect solution. Use solution within 48 hours.

3. Remove plastic tab covering center of stopper.

4. Sterilize top of stopper with a suitable germicide.

5. Insert needle squarely through center of stopper until tip is just visible, 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.

6.5 AVAILABILITY

Methylprednisolone sodium succinate (Solu-Medrol) 40 mg/mL vial: Box containing 1 Act-O-Vial, with diluent in upper compartment

Methylprednisolone sodium succinate (Solu-Medrol) 125 mg/2 mL vial: Box containing 1 Act-O-Vial, with diluent in upper compartment

Methylprednisolone sodium succinate (Solu-Medrol) 500 mg vial with 8 mL diluent

Methylprednisolone sodium succinate (Solu-Medrol) 1 g vial with 15.6 mL diluent

CAUTION: Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Manufactured by: 125 mg Powder for Injection (in Act-O-Vial), 500 mg Powder for Injection
Pharmacia & Upjohn Company, Kalamazoo, Michigan, U. S. A.

40 mg Powder for Injection (in Act-O-Vial), 1 g Powder for Injection
Pfizer Manufacturing Belgium NV, Puurs, Belgium

Rev. No.: 2.1
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Ref. Date: 31 October 2011