

**PRODUCT MONOGRAPH**

**methylPREDNISolone SODIUM SUCCINATE  
FOR INJECTION**

**USP**

methylPREDNISolone

Sterile Powder  
40mg, 125mg, 500 mg, 1 g, 5 g Vials

**Glucocorticoid/ Anti-Inflammatory**

Teva Canada Limited  
30 Novopharm Court  
Toronto, Ontario  
M1B 2K9

Date of Preparation:  
May 5, 2014

**Control No.:**173204

## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION.....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS.....	5
WARNINGS AND PRECAUTIONS.....	5
ADVERSE REACTIONS .....	10
DRUG INTERACTIONS.....	11
DOSAGE AND ADMINISTRATION.....	14
OVERDOSAGE .....	17
ACTION AND CLINICAL PHARMACOLOGY.....	17
STORAGE AND STABILITY.....	19
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	20
<b>PART II: SCIENTIFIC INFORMATION.....</b>	<b>21</b>
PHARMACEUTICAL INFORMATION .....	21
CLINICAL TRIALS.....	22
DETAILED PHARMACOLOGY.....	23
TOXICOLOGY.....	23
REFERENCES .....	24
<b>PART III: CONSUMER INFORMATION .....</b>	<b>26</b>

## PRODUCT MONOGRAPH

### methylPREDNISolone SODIUM SUCCINATE FOR INJECTION USP

methylPREDNISolone

### THERAPEUTIC CLASSIFICATION

Glucocorticoid/ Anti-Inflammatory

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
intravenous or intramuscular injection or by intravenous infusion	sterile powder 40 mg, 125 mg, 500 mg, 1 g, 5 g	Lactose Anhydrous <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

Intravenous administration of methylPREDNISolone sodium succinate is indicated in situations in which a rapid and intense hormonal effect is required. These include the following:

#### Hypersensitivity and dermatologic conditions

- Status asthmaticus
- Anaphylactic reactions (see text)
- Drug reactions
- Contact dermatitis
- Urticaria
- Generalized neurodermatitis
- Reactions to insect bites
- Pemphigus foliaceus and vulgaris
- Exfoliative dermatitis
- Erythema multiforme

### As Adjunctive therapy in

- Acute systemic lupus erythematosus
- Acute rheumatic fever
- Acute gout

### Ulcerative colitis

In addition to the above conditions, colonic instillation of methylPREDNISolone sodium succinate in retention enemas or by continuous drip, have been shown to be a useful adjunct in the treatment of patients with ulcerative colitis.

In anaphylactic reactions epinephrine or norepinephrine should be administered first for an immediate hemodynamic effect followed by intravenous injection of methylPREDNISolone sodium succinate and other accepted procedures. There is evidence that the corticoids through their prolonged hemodynamic effect are of value in preventing recurrent attacks of acute anaphylactic reactions.

In sensitivity reactions such as in serum sickness, allergic dermatosis (urticaria) and reactions to insect bites, methylPREDNISolone sodium succinate is capable of providing relief within 1/2 to 2 hours. In some asthmatic patients it may be advantageous to administer methylPREDNISolone sodium succinate by slow intravenous drip over a period of hours.

As adjunctive therapy in fulminating acute systemic lupus erythematosus and acute rheumatic fever, and to relieve pain during the acute manifestations of gout, methylPREDNISolone sodium succinate may be given by slow intravenous administration over a period of several minutes. Thereafter, the patient should be placed on intramuscular or oral therapy as required for continued relief of symptoms. In these conditions, other accepted measures of therapy should also be instituted.

### Shock

In severe hemorrhagic or traumatic shock, adjunctive use of intravenous methylPREDNISolone sodium succinate may aid in achieving hemodynamic restoration. Corticoid therapy should not replace standard methods of combating shock, but present evidence indicates that concurrent use of large doses of corticoids with other measures may improve survival rates.

### Organ transplants

Corticosteroids both, parenterally and orally, in high doses have been used following organ transplantation as part of multi-faceted attempts to reduce the rejection phenomenon. methylPREDNISolone sodium succinate is suitable for such indications.

### Cerebral edema of non traumatic origin

Corticosteroid therapy as an adjunct to the usual forms of therapy for cerebral edema has been used for many years. Cerebral edema associated with acute craniocerebral injuries and intracranial haematomas of traumatic origin, have been treated with methylPREDNISolone sodium succinate with some improvement in overall survival rate and reduction of permanent disability following such conditions. Administration of methylPREDNISolone sodium succinate

immediately prior to intracranial surgery and in the immediate post-operative period has reduced the duration of post-operative complications related to cerebral edema.

#### Acute spinal cord injury

The use of methylPREDNISolone sodium succinate in high doses has resulted in improvement in motor and sensory recovery. Treatment should begin within eight hours of injury.

### **CONTRAINDICATIONS**

methylPREDNISolone sodium succinate is contraindicated for untreated systemic fungal infections, with known hypersensitivity to methylPREDNISolone sodium succinate, any of its ingredients or other corticosteroids.

Except when used for short-term or emergency therapy as in acute sensitivity reactions, methylPREDNISolone sodium succinate is contraindicated in patients with arrested tuberculosis, herpes simplex keratitis, acute psychoses, Cushing's syndrome, peptic ulcer, markedly elevated serum creatinine, vaccinia and varicella. methylPREDNISolone sodium succinate is also contraindicated for systemic fungal infections and known hypersensitivity to the ingredients.

### **WARNINGS AND PRECAUTIONS**

#### **General**

methylPREDNISolone sodium succinate should not be used to treat head injury as demonstrated by the results of a multicenter study. The study results revealed an increased mortality in the 2 weeks after injury in patients administered methylPREDNISolone sodium succinate compared to placebo (1.18 relative risk).

Recent studies do not establish the efficacy of methylPREDNISolone sodium succinate in septic shock, and suggest that increased mortality may occur in some subgroups at higher risk (i.e. elevated serum creatinine greater than 2.0 mg/dL or secondary infections).

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 and as to whether daily or intermittent therapy should be used.

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

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts or glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of corticosteroids 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. While on corticosteroid therapy, patients should not be vaccinated against measles. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially high doses, because of possible hazards of neurological complications and lack of antibody response.

Patients should be advised to inform subsequent physicians of the prior use of methylPREDNISolone sodium succinate. The diluent for reconstitution of the Vials should be Bacteriostatic Water for Injection, which contains benzyl alcohol. Benzyl alcohol has been reported to be associated with fatal "Gasping Syndrome" in premature infants.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis of the liver.

Following prolonged therapy, psychological and/or physiological dependence may develop. Withdrawal of glucocorticoids may result in symptoms of the glucocorticoid withdrawal syndrome including: fever, myalgia, arthralgia and malaise. This may occur in patients even without evidence of adrenal insufficiency.

Aspirin (ASA) and other NSAIDs should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

In myasthenia gravis, hospitalization with careful observation is recommended because transient worsening of symptoms, possibly leading to respiratory distress may precede clinical improvement.

Patients should be warned not to discontinue the use of methylPREDNISolone sodium succinate abruptly or without medical supervision, to advise any medical attendants that they are receiving methylPREDNISolone sodium succinate and to seek medical advice at once should they develop fever or other signs of infection.

Corticosteroids 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.

Adequate adrenocortical supportive therapy including ACTH must be employed promptly if the patient is subjected to any unusual stress such as surgery, trauma or severe infection.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay (See WARNINGS).

Steroids may increase or decrease motility and number of spermatozoa in some male patients. However, it is not known whether reproductive capacity in humans is adversely affected.

### **Cardiovascular**

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

### **Endocrine and Metabolism**

Since methylprednisolone, like prednisolone, suppresses endogenous adrenocortical activity, it is highly important that the patient receiving methylPREDNISolone sodium succinate be under careful observation, not only during the course of treatment but for some time after treatment is terminated.

Glucocorticoid-induced suppression of HPA (Hypothalamic-Pituitary-Adrenal) function is dependent on dose and duration of treatment. Recovery occurs gradually as the steroid dose is reduced and withdrawn. Suppression persists for a period of time after withdrawal depending on dose and length of treatment time.

### **Gastrointestinal**

The existence of diabetes, osteoporosis, renal insufficiency, chronic psychosis, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, hypertension, myasthenia gravis or predisposition to thrombophlebitis requires that methylPREDNISolone sodium succinate be administered with extreme caution. The same caution should also be used in non-specific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infections.

### **Immune**

Corticosteroids 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 infections, 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 immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

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.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles can have a more serious or even fatal course in non-immune children or adults who are on corticosteroids. In such children or adults who

have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

The use of methylPREDNISolonesodium succinate 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.

Because rare instances of anaphylactoid (e.g. bronchospasm) reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

### **Neurologic**

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

An acute myopathy has been described 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 neuromuscular blocking drugs (e.g. 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.

### **Ophthalmologic**

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

### **Psychiatric**

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

### **Skin**

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.



During prolonged corticosteroid therapy, routine laboratory studies such as urinalysis, 2 hour postprandial blood sugar determinations, blood pressure monitoring, body weight and chest X-ray should be performed at regular intervals. If doses of methylPREDNISolone sodium succinate are high, serum potassium should be monitored regularly. Serious consideration of upper gastrointestinal studies should be contemplated when patients complain of gastric symptoms while on this medication.

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstated. Since mineralocorticoid secretion may be impaired, salt and/or mineralocorticoids should be administered concurrently.

### **Special Populations**

**Pregnant Women:** Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the use of this drug during pregnancy, in nursing mothers and women of childbearing potential, requires that the benefits of the drug be carefully weighed against the potential risk to the mother and embryo or fetus. Newborn infants of mothers who received such therapy during pregnancy should be observed for signs of hypoadrenalism and appropriate measures instituted if such signs are present. No effect is known upon labour and delivery.

**Nursing Women:** Because prednisolone is excreted in breast milk it is reasonable to assume that all corticosteroids are. No specific data are available for methylPREDNISolone sodium succinate.

**Pediatric Use:** Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Administration of corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen.

Pediatric patients demonstrate greater susceptibility to corticosteroid induced HPA axis suppression and Cushing's syndrome, than mature patients. HPA axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children taking oral corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papilloedema.

## ADVERSE REACTIONS

Corticosteroids have the potential for multiple adverse effects. There are essentially 2 types of toxicity observed when administered in therapeutic dosages: withdrawal effects, which could produce life-threatening adrenal insufficiency; and continuous high dosage over long periods, which could produce fluid/electrolyte disturbances, hyperglycemia, increased susceptibility to infections, peptic ulceration, osteoporosis, myopathy, behavioural disturbances, cataracts, or Cushing's habitus. Single doses, or short courses of therapy (over several days) usually produce less harmful effects. The approach to therapy should follow a logical and rational sequence of: (i) attempting to control the condition with more conventional mode(s) of management; (ii) weighing the benefits of steroid therapy against the risks; (iii) commencing therapy with a high loading dose, reducing to the minimum effective dosage as soon as possible.

The following Adverse Reactions have been reported with the systemic use of corticosteroid preparations methylPREDNISolone sodium succinate. Their inclusion in this list does not necessarily indicate that the specific event has been observed with methylPREDNISolone sodium succinate:

**Infections and Infestations:** masking of infections, latent infections becoming active, opportunistic infections

**Immune System Disorders:** hypersensitivity reactions, including anaphylaxis with or without circulatory collapse, cardiac arrest, bronchospasm, may suppress reactions to skin tests

**Endocrine Disorders:** development of Cushingoid state, suppression of pituitary-adrenal axis, suppression of growth in children

**Metabolism and Nutrition Disorders:** sodium retention, sodium excretion, fluid retention, diuresis, decreased carbohydrate tolerance, manifestation of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics, negative nitrogen balance due to proteincatabolism

**Psychiatric Disorders:** psychic derangements

**Nervous System Disorders:** increased intracranial pressure with papilloedema (pseudotumor cerebri), seizures

**Eye Disorders:** posterior subcapsular cataracts, exophthalmos, increased intraocular pressure

**Cardiac Disorders:** congestive heart failure in susceptible patients, myocardial rupture following a myocardial infarction, arrhythmia, hypertension, hypotension

**Vascular Disorders:** ecchymosis, petechiae

**Gastrointestinal Disorders:** peptic ulceration with possible perforation and hemorrhage, gastric hemorrhage, pancreatitis, esophagitis, perforation of the bowel, transient nausea, vomiting or dysgeusia (with rapid administration of large doses)

**Skin and Subcutaneous Tissue Disorders:** thin fragile skin, impaired wound healing

**Musculoskeletal and Connective Tissue Disorders:** steroid myopathy, muscle weakness, osteoporosis, aseptic necrosis, pathologic fractures, vertebral compression fractures, tendon rupture, particularly of the Achilles tendon

**Reproductive System and Breast Disorders:** menstrual irregularities

**Abnormal Hematological & Clinical Findings:** potassium loss with resulting hypokalemic alkalosis, sodium and fluid retention, increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase,

## **DRUG INTERACTIONS**

### **Overview**

CYP3A4 inhibitors (such as macrolides, triazole antifungals, and some calcium channel blockers) may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore the dose of methylprednisolone should be titrated to avoid steroid toxicity.

Anticholinesterase effects may be antagonized by glucocorticoids in myasthenia gravis. Toxicity may be enhanced when cyclosporin and glucocorticoids are combined in organ transplant patients. Co-administration with digitalis glycosides may enhance the possibility of digitalis toxicity associated with hypocalcemia. Isoniazid and salicylate serum concentrations may be decreased upon co-administration with glucocorticoids.

Potassium-depleting agents (eg. thiazide diuretics) may enhance hypocalcemia and hypokalemia secondary to glucocorticoid use. Co-administration with non-steroidal anti-inflammatories (NSAIDs) may increase the risk of gastrointestinal ulceration. Immunologic response to vaccines and toxoids is reduced by glucocorticoids which may also potentiate the replication of organisms in attenuated vaccines (e.g., measles). Glucocorticoids may alter laboratory or radiological tests for serum T<sub>3</sub> or serum protein-bound iodine, may decrease T<sub>4</sub> minimally or decrease the uptake of <sup>131</sup>iodine.

Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g., Addison's disease).

## Drug-Drug Interactions

The following table includes the common interactions seen with Solu-Medrol and other drug products. Methylprednisolone, like all glucocorticoids, can cause the following effects when administered in combination with these products. This table is meant to serve as a guide to professionals when considering a rational course of therapy.

<b>COMMON INTERACTIONS SEEN WITH SOLU-MEDROL AND OTHER DRUG PRODUCTS</b>				
<b>CLASS OF DRUG</b>	<b>DRUG(S) INVOLVED</b>	<b>AFFECTS THERAPY OF DRUG(S)</b>	<b>CLINICAL IMPLICATION</b>	<b>MECHANISM</b>
Antibiotic/ Antifungal Therapy	Troleandomycin Erythromycin Ketoconazole	Methylprednisolone	Enhanced clinical effects and side effects of methylprednisolone.	Enzyme inhibition: Reduced MP elimination.
	Rifampin	Methylprednisolone	May reduce efficacy; dosage adjustment may be required.	Enzyme induction, increased clearance.
Anticholinesterase	Neostigmine, Pyridostigmine	Anticholinesterase	Precipitation of myasthenic crisis.	
Anticoagulants	Oral Anticoagulants or Heparin	Anticoagulant	Increased or decreased clotting. Monitor response. Adjust dose	
Anticonvulsants	e.g. Phenobarbitone, Phenytoin	Methylprednisolone	May reduce methylprednisolone efficacy. Monitor clinical response. Adjust dose if necessary.	Enzyme induction: increased clearance of methylprednisolone
Antidiabetic Drugs	e.g. Insulin, Glibenclamide, Metformin	Antidiabetic	May impair glucose control. Monitor glucose levels and adjust dose of antidiabetic therapy.	Diabetogenic effects of corticosteroid.
Antihypertensive Agents	All Antihypertensives	Antihypertensive	May result in partial loss of hypertensive control.	Mineralocorticoid effect of corticosteroid leading to raised blood pressure.
Diuretics	All potassium losing Diuretics e.g. Furosemide		Enhanced toxicity. Monitor K <sup>+</sup> levels and supplement if necessary.	Potassium loss.
Cardioactive Drugs	Digoxin and related Glycosides	Digoxin	Potential of digoxin toxicity.	Corticosteroid induced potassium loss (mineralocorticoid effect)
Immunizing Agents	Live Vaccine: Poliomyelitis, BCG, Mumps, Measles, Rubella, Smallpox	Vaccine	May see increased toxicity from vaccine. Disseminated viral disease may occur.	Corticosteroid induced immunosuppression
	Killed Virulent Vaccines	Vaccine	Reduced response to vaccine.	Impaired immune response

<b>COMMON INTERACTIONS SEEN WITH SOLU-MEDROL AND OTHER DRUG PRODUCTS</b>						
<b>CLASS OF DRUG</b>	<b>OF</b>	<b>DRUG(S) INVOLVED</b>	<b>AFFECTS THERAPY OF DRUG(S)</b>	<b>OF</b>	<b>CLINICAL IMPLICATION</b>	<b>MECHANISM</b>
Immuno-suppressants		Methotrexate Azathioprine	Methylprednisolone Both		May allow reduced dose of corticosteroid.	Synergistic effect on disease state.
		Cyclosporin (CYA)			Monitor cyclosporin A levels. Adjust dose as necessary.	Mutual inhibition of metabolism.
Neuromuscular Blocking Agents		Pancuronium	Pancuronium		Partial reversal of neuromuscular block.	
Psychotherapeutic		Anxiolytics Antipsychotics	CNS active drug		Recurrence or poor control of CNS symptoms. May require dose adjustment.	CNS effects of corticosteroid.
Salicylates			Salicylate		Apparent decrease in salicylate efficacy or salicylate toxicity upon reduction of corticosteroid dose.	Increased clearance and decreased plasma level.
Sympathomimetic Agents		e.g. Salbutamol			Increased efficacy and potentially increased toxicity.	Increased response to sympathetic agents.

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

## **DOSAGE AND ADMINISTRATION**

The minimum effective dosage should be sought once clinical control of the disease is obtained. Withdrawal should be slow and gradual in order to avoid glucocorticoid withdrawal syndrome.

Dosage ranges for corticosteroids are extremely wide and patient responses are quite variable. Dosage should be individualized according to the diagnosis, severity, prognosis, probable duration of disease, patient response and tolerance. For infants and children, the recommended dosage should be governed by the same considerations rather than by strict adherence to the ratio indicated by age or body weight.

### **As adjunctive therapy in life-threatening conditions (e.g., shock states)**

The recommended dose of methylPREDNISolone sodium succinate is 30 mg/kg, given intravenously over a period of at least 30 minutes. The large doses may be repeated every 4 to 6 hours for up to 48 hours.

### **Acute Spinal Cord Injury:**

For treatment of acute spinal cord injury, administer intravenously 30 mg methylPREDNISolone sodium succinate per kg of body weight in a bolus dose over a 15 minute period, followed by a 45 minute pause, and then a continuous infusion of 5.4 mg/kg/hour for 23 hours. There should be a separate intravenous site for the infusion pump. The treatment should begin within 8 hours of injury.

### **Ulcerative Colitis:**

methylPREDNISolone sodium succinate in doses of 40 to 120 mg administered as retention enemas or by continuous drip 3 to 7 times weekly for periods of 2 or more weeks have been shown to be a useful adjunct in the treatment of some patients with ulcerative colitis. Many patients can be controlled with 40 mg administered in 30 - 300 mL of water depending on the degree of involvement of the inflamed colonic mucosa. Other accepted therapeutic measures should, of course, be instituted.

### **In other indications:**

Initial dosage will vary from 10 to 500 mg depending on the clinical problem being treated. Larger doses may be required for short-term management of severe, acute conditions. Therapy may be initiated by administering methylPREDNISolone sodium succinate intravenously over a period of at least 5 minutes (e.g., doses up to 250 mg) to at least 30 minutes (e.g., doses greater than 250 mg). Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical condition. Corticosteroid therapy is an adjunct to, and not replacement for, conventional therapy.

methylPREDNISolone sodium succinate may be administered by intravenous or intramuscular injection or by intravenous infusion. The preferred method for initial emergency use is intravenous injection. To administer by intravenous (or intramuscular) injection, prepare solution as directed (see DIRECTIONS FOR RECONSTITUTION).

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. 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 case as to dose and duration of treatment and whether daily or intermittent therapy should be used.

Alternate day therapy (ADT) in which a single dose is administered every other morning is the dosage regimen of choice for long-term corticosteroid treatment.

Morning administration of the drug simulates the natural circadian rhythm of corticosteroid secretion which is high in the morning and low in the evening. This regimen provides relief of symptoms while minimizing adrenal suppression, cushingoid state, withdrawal symptoms and growth suppression in children. Intermediate acting agents should be used for alternate day therapy (See the table below).

The following table provides a comparison of glucocorticoid equivalence.

<b>CORTICOSTEROID COMPARISON CHART</b>			
<b>Drug</b>	<b>Biologic Half-Life (Hours)</b>	<b>Equivalent Anti-inflammatory Dose (mg)*</b>	<b>Relative Mineralocorticoid Potency</b>
<b>Glucocorticoids:</b>			
<b>Short-acting</b>			
	8-12		
Cortisone		25	2
Hydrocortisone		20	2
<b>Intermediate acting</b>			
	18-36		
methylPREDNISolone		4	0
Prednisolone		5	1
Prednisone		5	1
Triamcinolone		4	0
<b>Long-acting</b>			
	36-54		
Betamethasone		0.6	0
Dexamethasone		0.75	0
<b>Mineralocorticoid:</b>			
Fludrocortisone	12-24	10	125

\*Equivalent doses are general approximations and may not apply to all diseases or routes of administration. Duration of HPA axis suppression and degree of mineralocorticoid activities must be considered separately.

**DIRECTIONS FOR RECONSTITUTION OF flip-top VIALS:**

1. Remove the protective plastic flip-top seal.
2. Swab the rubber stopper with an antiseptic solution and introduce the required quantity of the diluent by means of a syringe into the vial.
3. Shake the vial thoroughly to dissolve the powder content.
4. Withdraw the dose in the usual manner with the help of a syringe.

Reconstitute with Sterile Water for Injection, or, if required, Bacteriostatic Water for Injection as follows:

**RECONSTITUTION TABLE**

Size	Quantity of Diluent (mL)	Approx. Withdrawable Volume (mL)	Nominal Concentration (mg/mL)
40 mg/vial	1	1	40
125 mg/vial	2	2	62.5
500 mg/vial	7.8	8	62.5
1 g/vial	15.6	16	62.5
5 g/vial	78.0	80	62.5

The reconstituted and diluted solution should be inspected visually for discoloration, haziness, particulate matter and leakage prior to administration. Discard unused portion.

**Preparation of solution for IM or IV injection:**

Loosen powder. Hold vial horizontally and rotate while directing the stream of diluent against the wall of the vial. Shake vial gently after all the diluent is added. Use solution only if it is clear.

**Preparation of solutions for IV infusion:**

First prepare the solution for injection as directed.

If desired, the medication may be administered in dilute solutions by admixing the reconstituted product with Dextrose 5% in Water, 0.9% Sodium Chloride, Dextrose 5% in 0.45% Sodium Chloride. Concentrations of 0.25 mg/mL or less are physically and chemically stable for 48 hours at 15°C to 25°C.

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



## **Compatibility**

The compatibility and stability of methylPREDNISolone SODIUM SUCCINATE FOR INJECTION in solutions and with other drugs in intravenous admixtures is dependent on admixture pH, concentration, time, temperature, and ability of methylPREDNISolone to solubilize itself. Thus, to avoid compatibility and stability problems, whenever possible it is recommended that methylPREDNISolone SODIUM SUCCINATE FOR INJECTION be administered separately from other drugs and as either I.V. push, through an I.V. medication chamber, or as an I.V. “piggy-back” solution.

## **OVERDOSAGE**

There is no clinical symptom of acute overdosage with this drug. methylPREDNISolone sodium succinate is dialysable. The metabolism and excretion of methylPREDNISolone are similar to those of other corticosteroids. Continuous overdosage would require careful gradual reduction of dosage in order to prevent the occurrence of acute adrenal insufficiency.

For corticosteroids in general, anaphylactic and hypersensitivity reactions depending on their severity, may be treated with antihistamines with or without epinephrine.

In the absence of specific rescue therapy, treatment is to be symptomatic and supportive.

Since injections of slightly soluble corticosteroids may produce atrophy at the site of injection, i.m. injections of these products should be made deeply into gluteal muscle; repeated i.m. injections at the same site should be avoided and these products should not be administered s.c.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

methylPREDNISolone sodium succinate is a synthetic adrenocortical steroid derivative with predominantly glucocorticoid properties possessing anti-inflammatory and immunosuppressive action.

methylPREDNISolone sodium succinate belongs to the pharmacologic class of glucocorticoid/anti-inflammatory drugs which, following systemic absorption, diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes may enter the cell nucleus, bind to DNA and stimulate transcription of mRNA. Subsequent cellular responses result in a variety of local and systemic effects. Anti-inflammatory processes such as edema, fibrin deposition, decreased prostaglandin/thromboxane synthesis, capillary dilation, migration of leukocytes, phagocytosis stage of wound healing and cicatrization are inhibited. Immune reactions are suppressed. Metabolically, protein catabolism and increased gluconeogenesis along with decreased peripheral utilization of glucose leads to glycogen storage in the liver, increased blood glucose concentration and insulin resistance (diabetogenic effect). During therapy, lipolysis is enhanced and abnormal distribution of fat may result (Cushingoid effect). Skeletal

calcium is mobilized and lost via renal excretion. Glucocorticoids, in general, augment renal glomerular filtration and promote urate excretion.

Cortisone and prednisone are reduced to their pharmacologically active forms, hydrocortisone and prednisolone respectively. Pharmacologically active compounds are then metabolized primarily in the liver to biologically inactive compounds. Inactive metabolites, primarily glucuronides and sulfates are excreted by the kidneys. Small amounts of unmetabolized drug are excreted in urine and bile.

### **Pharmacokinetics**

Exceeding prednisolone in anti-inflammatory potency and having even less tendency than prednisolone to induce retention of sodium and water, methylPREDNISolone sodium succinate offers the use of lower doses with an enhanced split between anti-inflammatory and mineralocorticoid activities. Thus methylPREDNISolone sodium succinate may be indicated for emergency use in patients in whom increased sodium retention would be hazardous.

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. Studies indicate that the administration of methylPREDNISolone results in an appreciable prolongation of plasma steroid levels over those obtained following equivalent doses of hydrocortisone or prednisolone. The following table illustrates this prolongation of blood levels expressed as the half-life in minutes of the 17-hydroxy-corticosteroid levels obtained following intravenous administration of methylPREDNISolone, prednisolone and hydrocortisone.

<b>COMPOUND</b>	<b>DOSE</b>	<b>HALF-LIFE (minutes)</b>
methylPREDNISolone	25 mg	188
Prednisolone	25 mg	69
Hydrocortisone	25 mg	57

## **STORAGE AND STABILITY**

### Unreconstituted Product:

Store at controlled room temperature 15°C to 25°C, protect from light.

### Reconstituted Solutions:

Store at controlled room temperature 15°C to 25°C, protect from light.

When reconstituted with Sterile Water for Injection, (without bacteriostat), use as a **single use vial**. Use solution within 24 hours after mixing; **discard unused solution**.

Only facilities with recognized admixture programmes, where dilutions are performed under aseptic conditions, should store the diluted product for more than 24 hours after initial puncture of the stopper particularly if Sterile Water For Injection is used as the reconstitution vehicle.

When reconstituted with Bacteriostatic Water for Injection, stored at controlled room temperature (15°C to 25°C), protected from light. The 40 mg vials, 125 mg vials, 500 mg vials, 1 g vials and the 5 g vials, reconstituted as indicated in the Reconstitution Table below, should be used within 48 hours. **Discard unused solution**.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

methylPREDNISolone SODIUM SUCCINATE FOR INJECTION is a sterile, lyophilized powder available as 40 mg (Box of 10 vials), 125 mg (Box of 10 vials), and 500 mg (Box of 5 vials) strengths of methylPREDNISolone per vial, and in 1 g and 5 g of methylPREDNISolone per vial (Single vials).

The respective vials of methylPREDNISolone SODIUM SUCCINATE FOR INJECTION contain:

Ingredients	40 mg	125 mg	500 mg	1 g	5 g
methylPREDNISolone (mg/vial)	40.0 mg	125.0 mg	500.0 mg	1000.0 mg	5000.0 mg
(as methylPREDNISolone sodium succinate)	53.0 mg	166.0 mg	663.0 mg	1325.0 mg	6625.0 mg
Monobasic Sodium Phosphate USP, anhydrous	2.4 mg	1.93 mg	7.7 mg	15.4 mg	77.0 mg
Dibasic Sodium Phosphate USP, anhydrous	22.5 mg	18.28 mg	73.1 mg	146.2 mg	731.0 mg
Lactose NF, anhydrous	30.6 mg	0	0	0	0
Sodium Hydroxide, NF	qs to pH	qs to pH	qs to pH	qs to pH	qs to pH
Water for Injection, USP ***	qs	qs	qs	qs	qs

\*\*\*Water is required in the manufacture of the bulk solution but is removed during the lyophilization process.

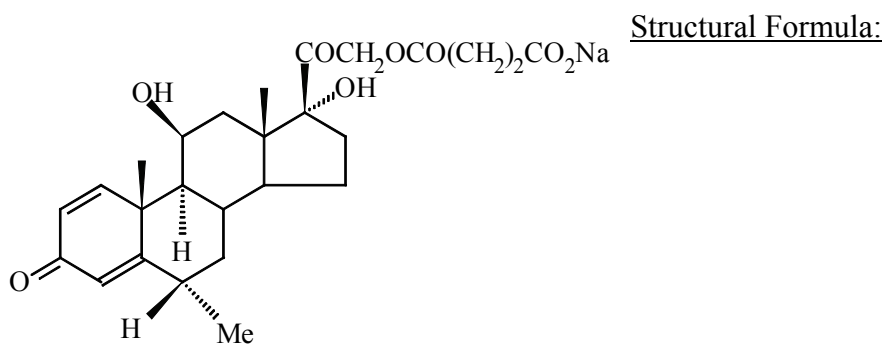
## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper Name: methylPREDNISolone sodium succinate (made in-situ from methylPREDNISolone hemisuccinate with the aid of sodium hydroxide)

Chemical Name: pregna-1,4-diene-3,20-dione, 21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-6-methyl-monosodium salt, (6,11)



Molecular Formula: C<sub>26</sub>H<sub>33</sub>NaO<sub>8</sub>

Molecular Weight: 496.53 g/mol

Description: methylPREDNISolone sodium succinate is a white or nearly white odourless, hygroscopic amorphous solid, mp (228° to 237°C), pKa of 4.6, partition coefficient (butyronitrile-water) of 0.03 at pH 8.5, very soluble in water and in alcohol, slightly soluble in acetone and practically insoluble in chloroform and ether.

## **CLINICAL TRIALS**

### **Hypersensitivity and Dermatologic Conditions**

#### **Status Asthmaticus**

In a double-blind, placebo-controlled, randomized trial, the use of intravenous methylprednisolone (125 mg), given on presentation in the emergency room in addition to standard emergency treatments for asthma, reduced the need for hospital admission in acutely ill patients with bronchial asthma. Nine of 48 patients (19 percent) treated with methylprednisolone required hospital admission compared with 23 of 49 patients (47 percent) in the control group ( $p < 0.003$ ).

#### **Pemphigus Vulgaris**

A small ( $n=15$ ) retrospective study compared high-dose pulsed methylprednisolone sodium succinate to oral prednisone in patients with pemphigus vulgaris. Methylprednisolone sodium succinate was administered intravenously ( $n=9$ ); the dose varied from 250 to 1000 mg/day for 2 to 5 days. Four of 6 responders to methylprednisolone sodium succinate maintained a remission without prednisone for almost 2 years. Patients in the control group ( $n=6$ ) treated with prednisone required long-term treatment with higher doses of prednisone, and none of the patients maintained a long-term remission.

#### **Acute Systemic Lupus Erythematosus**

High-dose, intravenous methylprednisolone pulse therapy in 34 patients (30 adults and 4 adolescents) with lupus nephritis was evaluated. The 30 adult patients received 1 g of methylprednisolone intravenously over 30 minutes on 3 successive days, while the 4 adolescents received a 15 mg/kg/day dose for 3 days. Twelve of the 34 patients responded to treatment, as indicated by at least a 20% improvement in renal function and corresponding improvement in creatinine clearance levels. These improvements were maintained for at least 6 months in 60% of patients who responded to treatment.

#### **Ulcerative Colitis**

In a prospective, single-blind study of 60 patients with active ulcerative colitis, patients were randomized to receive either sucralfate enemas (20 g/100 ml) or methylprednisolone enemas (20 mg/100 ml). The enemas were administered twice daily for the first week and then once daily for three weeks. Results showed similar reductions in diarrhea and rectal bleeding at two weeks and at four weeks in the two groups. Sigmoidoscopic examination of the rectal mucosa demonstrated similar significant improvement in the macroscopic appearance of the rectal mucosa in both groups (8.28 to 6.20 in sucralfate group,  $p < 0.02$ ; and 8.72 to 6.36 in the methylprednisolone treated group,  $p < 0.04$ ). Histological assessment of the rectal biopsies taken at entry into the study and following four weeks of therapy also revealed similar improvements in the two groups.

## **Organ Transplants**

A prospective, controlled study was conducted among 100 renal transplant patients to compare two different regimens of immunosuppressive therapy. In the study, 86 patients received kidneys from cadavers and 14 patients received kidneys from living, related donors. Patients were assigned to receive either double therapy (methylprednisolone plus cyclosporine) or triple therapy (methylprednisolone plus cyclosporine and azathioprine). In both groups, patients were given intravenous pulse doses of 0.5 g methylprednisolone at the moment of transplantation. Oral methylprednisolone was subsequently administered in a single morning dose of 16 mg until the end of the third month. Patients then received 12 mg/day oral methylprednisolone until the end of month 6, and a maintenance dosage of 8 mg/day thereafter. The results were similar with both regimens. No significant differences between groups were reported in the 2-year patient and kidney survival rates.

## **DETAILED PHARMACOLOGY**

See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics** and **Pharmacokinetics** sections.

## **TOXICOLOGY**

The acute LD50 of methylprednisolone sodium succinate intraperitoneally in the mouse is 850 mg/kg. The oral LD50 of this drug in the rat is 5150 mg/kg. Dogs receiving single intravenous injections of methylprednisolone sodium succinate in doses of 4.4 to 6.4 mg/kg were free from clinical signs of drug intoxication during the 24 hour post-injection observation period.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

There is no evidence that corticosteroids are carcinogenic, mutagenic, or impair fertility.

## REFERENCES

1. AHFS, 1994, Adrenals, 68:04, Corticosteroids, (American Hospital of Pharmacists, Bethesda), 1980-1988 and 1999.
2. Blinderman EE, Graf CJ, Fitzpatrick T. Basic studies in cerebral edema - Its control by a corticosteroid (Solu-Medrol). J Neurosurg 1962; XIX (4):319-24.
3. Bracken MB, Shepard M, Collins WF et al. A randomized, controlled trial of methylPREDNISolone or naloxone in the treatment of acute spinal-cord injury: Results of the second national acute spinal cord injury study. New Eng J Med 1990;322(20):1405-11.
4. Burkle WS. Cyclosporin pharmacokinetics and blood level monitoring. Drug Intell Clin Pharm 1985;19:101-5.
5. Cowley RA, Trump BF. Pathophysiology of shock, anoxia and ischemia. Baltimore, MD. Williams and Wilkins 1982;692-3.
6. Dietzman RH, Bloch JH, Lillehei RC. Treatment of shock. GP 1967;36(3):135-41.
7. Dietzman RH, Manax WG, Lillehei RC. Shock: Mechanism and Therapy, Can Anaes Soc J 1967;14(4):276-86.
8. Dugger JA. Parenteral methylPREDNISolone acetate in management of allergy and contact dermatitis in children. Clinical Medicine 1962;69(10):2253-7.
9. Fox JL. Use of methylPREDNISolone in intracranial surgery. Medical Annals of District of Columbia 1965;34(6):261-6.
10. Goldberg LC. Routine use of intravenous 6-methylPREDNISolone. Journal of Michigan State Medical Society 1960;59:1049-51.
11. Leake GC, Pascale VJ, Alfano SL. methylPREDNISolone for acute spinal cord injury. Am J Hosp Pharm 1990;47:1977-8.
12. Lillehei RC, Longerbeam JK, Bloch JH, Manax WG. The modern treatment of shock based on physiologic principals. Clin Pharmacol Ther 1964;5(1):63-101.
13. Lillehei RC, Longerbeam JK, Bloch JH, Manax WG. The nature of irreversible shock: Experimental and clinical observations Ann Surg 1964;160(4):682-710.
14. Marcus PS, Sheehan JC, Comunale FL. Corticosteroids in hypovolemic shock. Anesthesiology, Dept. of Anesthesiology, Boston City Hospital 1966;27(2):221.



15. Martyndale (30th), The extra pharmacopoeia, Reynolds, JEF, editor, (The Pharmaceutical Press), 736-737 and 712-723.
16. Melby JC. Corticosteroids in shock in man and in animals. *The New Physician* 1964;13:425-8.
17. Robins J. Modern Concepts in the management of shock. *Obstet Gynecol (View and Reviews Section)* 1966;28(1):130-8.
18. Siegal, S. C., Overview of Corticosteroid Therapy, *J. Aller.Clin. Immun.*, 1985, 312-320.
19. Sparacio RR, Lin T. Cook AW. methylPREDNISolone sodium succinate in acute craniocerebral trauma. *Surg Gynecol Obstet* 1965;121:513-6.
20. Speed Rogers J. Hudson FM. Parenteral corticosteroids in the management of acute brain stem injuries. *WV Med J* 1963;59(8):18-20.
21. Stinson EB, Dong E Jr, Bieber CP, Schroeder S, Shumway NE. Cardiac Transplantation in Man. I. Early Rejection. *JAMA* 1969;207(12):2233-47.
22. Stubbs SS, Morrell RM. Intravenous methylPREDNISolone sodium succinate: Adverse reactions reported in association with immunosuppressive therapy. *Transplantation Proceedings* 1973;5(2):1145-6.
23. Turcotte JG, et al. Rejection crises in human renal transplant recipients. *Arch Surg* 1972;105:230-6.
24. Turlapaty PDMV, Altura BM. Extracellular magnesium ions control calcium exchange and content of vascular smooth muscle. *Eur J Pharmacol* 1978;52(3-4):421-3.
25. Weissman G, Thomas L. The effects of corticosteroids upon connective tissue and lysosomes. *Recent Prog Horm Res* 1964;20:215-45.
26. Wilson RD, Steroids stem ÒBurn Lung SyndromeÓ. *Medical News Section, JAMA* 1969;208(1):26.
27. Woods JE, et al. High-dosage intravenously administered methylPREDNISolone in renal transplantation. *JAMA* 1973;223(8):896-9.
28. Zahony I., Winnie AP, Collins VJ. Delayed postoperative effects of antihypertensive therapy. *Illinois Medical Journal* 1962;Aug:155-8.
29. SOLU-MEDROL<sup>®</sup> Product Monograph by TM Pfizer Enterprises SARL, Pfizer Canada Inc, Licensee Date of Revision: May 11, 2011, Control Number: 137885.

## IMPORTANT: PLEASE READ

### PART III: CONSUMER INFORMATION

#### **methylPREDNISolone sodium succinate for injection USP**

**This leaflet is part III of a three-part "Product Monograph" published when ethylPREDNISolone sodium succinate was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about methylPREDNISolone sodium succinate. Contact your doctor or pharmacist if you have any questions about the drug.**

#### **ABOUT THIS MEDICATION**

##### **What the medication is used for:**

methylPREDNISolone sodium succinate is used to relieve inflammation (swelling, heat, redness, and pain) caused by various conditions. For example, symptoms of inflammation are often seen with allergic reactions such as severe allergic skin reactions, reactions to insect bites, and anaphylaxis (a severe, life-threatening allergic reaction).

Other conditions treated with methylPREDNISolone sodium succinate include: relief of asthma symptoms caused by inflamed breathing passages, severe skin diseases, and ulcerative colitis (an intestinal disorder). methylPREDNISolone sodium succinate is also used for the prevention of rejection of organ transplants. methylPREDNISolone sodium succinate can be used in combination with other drugs (short term treatment) in some forms of arthritis. methylPREDNISolone sodium succinate can also be used in some surgical procedures.

##### **What it does:**

methylPREDNISolone sodium succinate belongs to a group of medicines known as corticosteroids. methylPREDNISolone sodium succinate is a synthetic corticosteroid and is usually used for short periods in severe conditions to decrease inflammation.

##### **When it should not be used:**

Except for short-term or emergency use such as severe allergic reactions, methylPREDNISolone sodium succinate should not be given to patients with:

- viral diseases including vaccinia (cowpox), varicella (chickenpox), and herpes simplex of the eye
- fungal infections
- tuberculosis

- serious mental disorder (psychoses)
- Cushing's syndrome (abnormal bodily condition caused by excess corticosteroids)
- a stomach ulcer
- altered kidney function-

methylPREDNISolone sodium succinate should not be given to patients who are allergic to this medicine or any ingredient of this medication.

##### **What the medicinal ingredient is:**

methylprednisolone sodium succinate

##### **What the important nonmedicinal ingredients are:**

Lactose hydrous. methylPREDNISolone sodium succinate also contains the following nonmedicinal ingredients: dibasic sodium phosphate dried and monobasic sodium phosphate anhydrous. When needed, the pH is adjusted with sodium hydroxide.

##### **What dosage forms it comes in:**

methylPREDNISolone sodium succinate comes in vials containing sterile powder for intravenous or intramuscular injection or for intravenous infusion. The available formulations are:

- 40 mg per vial
- 125 mg per vial
- 500 mg per vial
- 1 g per vial
- 5 g per vial

#### **WARNINGS AND PRECAUTIONS**

##### **BEFORE you use SOLU-MEDROL talk to your doctor or pharmacist:**

- if you have had tuberculosis or any other recent infections.
- if you have or have ever had liver, kidney, intestinal, or heart
- disease; diabetes; an underactive thyroid gland; high blood
- pressure; mental illness; myasthenia gravis (a disease
- causing muscle weakness); osteoporosis; herpes eye
- infection; seizures; or ulcers.
- if you are pregnant, planning to become pregnant or are
- breast-feeding (nursing).

## IMPORTANT: PLEASE READ

- if you have any allergies to this medicine or to any of the
- ingredients of this medication.
- if you had any prior use of methylPREDNISolone sodium succinate.

## INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about all prescription and non-prescription medications you are using. It is especially important that your doctor or pharmacist know if you are taking medication from the following categories of drugs:

- Antibiotics/Antifungals (e.g. rifampin and ketoconazole)
- Anticholinesterase (drugs that prevent the elimination of a neurotransmitter, acetylcholine. e.g. neostigmine and pyridostigmine)
- Drugs that prevent blood clotting (e.g. warfarin or heparin)
- Epilepsy medication (e.g. phenytoin)
- Diabetes medication (e.g. insulin or metformin)
- High blood pressure treatment (e.g. amlodipine or quinapril)
- Diuretics (e.g. furosemide)
- Heart medication (e.g. digoxin)
- Vaccines
- Drugs that suppress the immune system (methotrexate or cyclosporin)
- Neuromuscular Blocking Agents (agents that block signals between nerves and muscles. e.g. pancuronium)
- Drugs that act on the nervous system (e.g. diazepam or clozapine)
- Salicylates (e.g. aspirin)
- Sympathomimetic Agents (agents that mimic the effects of adrenaline. e.g. salbutamol)

## PROPER USE OF THIS MEDICATION

methylPREDNISolone sodium succinate may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection. To administer intravenous (or intramuscular) injection, the solution is prepared as follows:

### DIRECTIONS FOR USING THE methylPREDNISolone sodium succinate

1. Remove the protective plastic flip-top seal.
2. Swab the rubber stopper with an antiseptic solution and introduce the required quantity of the diluent by means of a syringe into the vial.
3. Shake the vial thoroughly to dissolve the powder content.
4. Withdraw the dose in the usual manner with the help of a syringe.

Reconstitute with Sterile Water for Injection, or, if required, Bacteriostatic Water for Injection

### Usual dose:

Initial dosage will vary from 10 to 500 mg depending on the clinical problem being treated. Larger doses may be required for short-term management of severe, acute conditions. Therapy may be initiated by administering methylPREDNISolone sodium succinate intravenously over a period of at least 5 minutes (e.g., doses up to 250 mg) to at least 30 minutes (e.g., doses greater than 250 mg). Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical condition. Corticosteroid therapy is used in combination with, and not replacement for, conventional therapy. The dose needs to be gradually decreased when the medication needs to be discontinued after several days of treatment.

### Overdose:

There is no easily noticeable symptom of an acute overdose of methylPREDNISolone sodium succinate. If an overdose occurs, methylPREDNISolone sodium succinate can be eliminated through dialysis. Continuous overdosing would require careful gradual reduction of the dose of the medication in order to prevent the occurrence of a condition where the body would be unable to normally produce certain hormones.

**IMPORTANT: PLEASE READ**

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

The following side effects have been reported with the systemic use of corticosteroid preparations such as methylPREDNISolone sodium succinate. Their inclusion below does not necessarily mean that the specific event has been observed with methylPREDNISolone sodium succinate.

methylPREDNISolone sodium succinate may hide symptoms of infections, may cause latent infections becoming active, may induce infections by normally inoffensive organisms due to lowered body resistance.

Immune System Disorders: allergic reactions, including anaphylaxis (a severe, life-threatening allergic reaction), cardiac arrest, bronchospasm (airway constriction), suppression of reactions to skin tests.

Endocrine Disorders: development of Cushingoid state (abnormal bodily condition caused by excess corticosteroids), suppression of pituitary-adrenal axis (a condition that could lead to disabling the body's responses to physiological stress such as severe infections or trauma), suppression of growth in children.

Metabolism and Nutrition Disorders: sodium retention and excretion, fluid retention, increased urination, decreased carbohydrate tolerance, manifestation of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics, negative nitrogen balance due to protein breakdown.

Psychiatric Disorders: mental illness.

Nervous System Disorders: increased pressure within the skull with edema and inflammation of the optic nerve, seizures.

Eye Disorders: cataracts, protrusion of the eyeball, increased intraocular pressure.

Cardiac Disorders: heart failure, heart attack, arrhythmia (irregular heartbeat), high and low blood pressure.

Vascular Disorders: ecchymosis (spots caused by ruptured blood vessels), petechiae (reddish spot containing blood that appears in skin).

Gastrointestinal Disorders: stomach ulcer, stomach bleeding, inflammation of the pancreas and esophagus, perforation of the bowel, nausea, vomiting or altered sense of taste (with rapid administration of large doses).

Skin and Subcutaneous Tissue Disorders: thin fragile skin, impaired wound healing

Musculoskeletal and Connective Tissue Disorders: muscle disease, muscle weakness, osteoporosis, aseptic necrosis (tissue death), pathologic fractures, vertebral compression fractures, tendon rupture, particularly of the Achilles tendon.

Reproductive System and Breast Disorders: menstrual irregularities.

methylPREDNISolone sodium succinate may cause abnormal blood and liver tests as well as, sodium and fluid retention.

**SERIOUS SIDE EFFECTS HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect	Talk with your doctor or pharmacist	Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases
infections		✓
increased in blood sugar	✓	
mental illness	✓	
seizures		✓
increased pressure inside the skull with edema and inflammation of the optic nerve	✓	
cataract (clouding of the lens)	✓	
cardiac disorders		✓
muscle and bone disease	✓	
allergic reaction*		✓

\*An allergic reaction can be a rash, itching, a swollen face, swollen lips or shortness of breath. If this ever happens to you, discontinue methylPREDNISolone

## IMPORTANT: PLEASE READ

sodium succinate and notify your doctor or pharmacist.

**Before Reconstitution:** Store methylPREDNISolone sodium succinate Sterile Powder at room temperature (15°C - 25°C). Protect from light. Keep out of the reach of children

**After Reconstitution:** Store reconstituted solution at room temperature (15°C - 25°C). Use reconstituted solution within 24 hours after mixing Sterile Water for Injection, (without bacteriostatic) and 48 hours after mixing with Bacteriostatic Water for Injection. Protect from light. Keep out of the reach of children

### **REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

***NOTE: Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

### **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:  
1-800-268-4127 ext. 5005 (English);  
1-877-777-9117 (French)  
or [druginfo@tevacanada.com](mailto:druginfo@tevacanada.com)

This leaflet was prepared by:  
Teva Canada Limited  
30 Novopharm Court  
Toronto, Ontario  
M1B 2K9  
Canada  
[www.tevacanada.com](http://www.tevacanada.com)

Last revised: May 5, 2014