PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]methylPREDNISolone SODIUM SUCCINATE FOR INJECTION

Methylprednisolone Sodium Succinate for Injection

Sterile Powder for Solution, 40mg, 125mg, 500 mg, 1 g Vials, intravenous or intramuscular

USP

Glucocorticoid

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Submission Control Number: 263266

Date of Initial Authorization:
MAY 06, 2014

Date of Revision:
September 23, 2022

RECENT MAJOR LABEL CHANGES

WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics	09/2022

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Intravenous administration of Methylprednisolone Sodium Succinate for Injection (methylprednisolone sodium succinate) is indicated in situations in which a rapid and intense hormonal effect is required.

Methylprednisolone Sodium Succinate for Injection is indicated for:

- Hypersensitivity and dermatologic conditions
  - Status asthmaticus
  - Anaphylactic reactions
  - Drug reactions
  - Contact dermatitis
  - Urticaria
  - Generalized neurodermatitis
  - Reactions to insect bites
  - Pemphigus foliaceous and vulgaris
  - Exfoliative dermatitis
  - Erythema multiforme

    - In anaphylactic reactions epinephrine or norepinephrine should be administered first for an immediate hemodynamic effect followed by intravenous injection of Methylprednisolone Sodium Succinate for Injection 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 for Injection is capable of providing relief within 1/2 to 2 hours. In some asthmatic patients it may be advantageous to administer Methylprednisolone Sodium Succinate for Injection by slow intravenous drip over a period of hours.

- As adjunctive therapy in
  - Acute systemic lupus erythematosus
  - Acute rheumatic fever
  - Acute gout

  In these conditions Methylprednisolone Sodium Succinate for Injection 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.

- Ulcerative colitis
  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.

- Shock
  In severe hemorrhagic or traumatic shock, adjunctive use of intravenous Methylprednisolone Sodium Succinate for Injection 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 for Injection is suitable for such indications.

- Cerebral oedema of non traumatic origin
  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 oedema.

1.1 Pediatrics

Methylprednisolone Sodium Succinate for Injection is contraindicated for use in premature infants (see 2 CONTRAINDICATIONS) and should be used with caution in the pediatric population (see 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics).

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

Methylprednisolone Sodium Succinate for Injection is contraindicated:

- in patients with known hypersensitivity to the ingredients. Methylprednisolone Sodium Succinate for Injection, 40 mg, include lactose produced from cow's milk. This dosage form is therefore contraindicated in patients with a known or suspected hypersensitivity to cow's milk or its components or other dairy products because it may contain trace amounts of milk ingredients.
- for systemic fungal infections
- in patients administered with live or live, attenuated vaccines while receiving immunosuppressive doses of corticosteroids.

- for intrathecal or epidural administration. Reports of serious medical events have been associated with these routes of administration.
- for use in premature infants, as the Bacteriostatic Water for Injection that is indicated for reconstituting Methylprednisolone Sodium Succinate for Injection products contains benzyl alcohol. See 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics
- for intramuscular administration in idiopathic thrombocytopenic purpura.

Except for short-term emergency therapy, Methylprednisolone Sodium Succinate for Injection is contraindicated in patients with:

- arrested tuberculosis
- herpes simplex keratitis
- acute psychoses
- Cushing's syndrome
- peptic ulcer
- markedly elevated serum creatinine
- vaccinia and varicella

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Because complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

- The lowest possible dose of corticosteroid should be used to control the condition under treatment.

- Patients should be advised to inform subsequent health professionals of the prior use of methylprednisolone sodium succinate.

- The existence of diabetes, osteoporosis, renal insufficiency, chronic psychosis, cardiovascular disease, myasthenia gravis or predisposition to thrombophlebitis requires that Methylprednisolone Sodium Succinate for Injection be administered with extreme caution.

- Dosage adjustments may be required based on the following:
  - during remission
  - exacerbation of the disease process
  - the patient's individual response to therapy

- upon exposure of the patient to emotional or physical stress such as serious infection, surgery or injury. Methylprednisolone Sodium Succinate for Injection dosage may need to be increased during and after the stressful situation.

- ***Geriatrics***: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

- Caution is recommended with prolonged corticosteroid treatment in the elderly due to a potential increased risk for osteoporosis, as well as increased risk for fluid retention with possible resultant hypertension.

- ***Pediatrics***: Methylprednisolone Sodium Succinate for Injection is contraindicated for use in premature infants (see 2 CONTRAINDICATIONS) and should be used with caution in the pediatric population (see 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics).

4.2 Recommended Dose and Dosage Adjustment

- Corticosteroid therapy is an adjunct to, and not replacement for, conventional therapy.

- As adjunctive therapy in life-threatening conditions (e.g., shock states), the recommended dose of Methylprednisolone Sodium Succinate for Injection is 30 mg per kg, given intravenously over a period of at least 30 minutes. This large dose may be repeated every 4 - 6 hours for up to 48 hours.

- 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 for Injection 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.

- Methylprednisolone Sodium Succinate for Injection in doses of 40 to 120 mg administered as retention enemas or by continuous drip three to seven times weekly for periods of two 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 of methylprednisolone sodium succinate administered in from 1 to 10 fluid ounces of water depending on the degree of involvement of the inflamed colonic mucosa. Other accepted therapeutic measures should, of course, be instituted.

4.3 Reconstitution

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

The reconstituted and diluted solution should be inspected visually for discolouration, 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 particulate matter and discolouration, 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 separate from other drugs and as either I.V. push, through an I.V. medication chamber, or as an I.V. "piggy-back" solution.

4.4 Administration

Methylprednisolone Sodium Succinate for Injection may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection.

To administer Methylprednisolone Sodium Succinate for Injection, reconstitute the vial as per instructions.

5 OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy.

For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced. Continuous overdosage would require careful gradual reduction of dosage in order to prevent the occurrence of acute adrenal insufficiency.

Methylprednisolone is dialyzable.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
intravenous or intramuscular injection or by intravenous infusion	sterile powder 40 mg, 125 mg, 500 mg, 1 g	40mg, 125mg, 500mg, and 1g: Monobasic Sodium Phosphate, Dibasic Sodium Phosphate, Sodium Hydroxide, Water for Injection 40mg only: Lactose

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 of methylprednisolone per vial (Single vial).

The respective vials of methylPREDNISolone SODIUM SUCCINATE FOR INJECTION contain:

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

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

7 WARNINGS AND PRECAUTIONS

General

Methylprednisolone Sodium Succinate for Injection should not be administered by any route other than those listed under 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING. It is critical that, during administration of Methylprednisolone Sodium Succinate for Injection, appropriate technique be used and care taken to assure proper route of administration.

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

Patients should be advised to inform subsequent health professionals of the prior use of methylprednisolone sodium succinate.

The slower rate of absorption by intramuscular administration should be recognized.

Carcinogenesis and Mutagenesis

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

Animal studies found corticosteroids to have possible tumorigenic and mutagenic potential (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenesis and Mutagenesis).

Cardiovascular

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 (greater 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.

Literature reports suggest an apparent association between the use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

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

As sodium retention with resultant oedema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution, and only if strictly necessary, in patients with congestive heart failure. Corticosteroids should be used with caution in hypertension, or renal insufficiency. See also 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.

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.

Driving and Operating Machinery

Dizziness, vertigo, visual disturbances and fatigue are possible side effects associated with corticosteroid use. If affected, patients should not drive or operate machinery

Endocrine and Metabolism

Corticosteroid administration 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. 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 may need to be reinstituted.

Acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

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

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. See also 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

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

There is an enhanced effect of corticosteroids in patients with hypothyroidism. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

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

Gastrointestinal

Corticosteroids should be used with caution in non-specific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection and in diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer, since they may increase the risk of a perforation. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

Glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. In combination with NSAIDs, such as Aspirin (acetylsalicylic acid), the risk of developing gastrointestinal ulcers is increased.

Hematologic

Aspirin (acetylsalicylic acid) should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Hepatic/Biliary/Pancreatic

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

There is an enhanced effect of corticosteroids in patients with cirrhosis.

High doses of corticosteroids may produce acute pancreatitis.

Immune

Corticosteroids may suppress the immune system and 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 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.

Recent studies suggest that corticosteroids should not be used in septic shock (an unapproved indication), and suggest that increased mortality may occur in some subgroups at higher risk (e.g., elevated serum creatinine greater than 2.0 mg/dL or secondary infections).

Do not use intra-articularly, intrabursally or for intratendinous administration for local effect in the presence of acute local infection.

Fungal infections
Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure. See also 2 CONTRAINDICATIONS; 9 DRUG INTERACTIONS.

Special pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

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

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

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.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see 2 CONTRAINDICATIONS). Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non immunosuppressive doses of corticosteroids.

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

Viral infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients 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 also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Recent studies do not support Methylprednisolone Sodium Succinate for Injection use during septic shock, and suggest that increased mortality may occur in some subgroups at higher risk (e.g., elevated serum creatinine greater than 2.0 mg/dL or secondary infections).

Monitoring and Laboratory Tests

Corticosteroids may suppress reactions to skin tests.

Since methylprednisolone suppresses endogenous adrenocortical activity, it is highly important that the patient receiving Methylprednisolone Sodium Succinate for Injection be under careful observation, not only during the course of treatment but for some time after treatment is terminated. Monitoring for signs and symptoms of drug-induced secondary adrenocortical insufficiency may be necessary for up to one year following cessation of long-term or high-dose corticosteroid therapy.

Musculoskeletal

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g. myasthenia gravis, see 7 WARNINGS AND PRECAUTIONS - Neurologic), or in patients receiving concomitant therapy with anticholinergics such as neuromuscular blocking drugs (e.g. pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (e.g., postmenopausal women) before initiating corticosteroid therapy.

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

Neurologic

Convulsions have been reported with concurrent use of methylprednisolone and 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.

Systemic corticosteroids are not indicated for, and therefore should not be used to treat traumatic brain injury. A multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo.

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

Corticosteroids should be used with caution in patients with myasthenia gravis.

There have been reports of epidural lipomatosis in patients taking corticosteroids (including reports in children).

Ophthalmologic

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, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

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.

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.

Renal

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

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

Reproductive Health: Female and Male Potential

- **Fertility**

Steroids may increase or decrease motility and number of spermatozoa in some patients (see 16 NON-CLINICAL TOXICOLOGY).

Sensitivity/Resistance

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.

In patients receiving 40 mg Methylprednisolone Sodium Succinate for Injection during the treatment for acute allergic conditions and where these symptoms worsen or any new allergic symptoms occur, consideration should be given to the potential for hypersensitivity reactions to cow's milk ingredients (see 2 CONTRAINDICATIONS). If appropriate, administration of methylprednisolone sodium succinate should be stopped, and the patient's condition should be treated accordingly. Alternative treatments, including the use of corticosteroid formulations that do not contain ingredients produced from cow's milk, should be considered for acute allergy management, where appropriate.

Skin

Injection of Methylprednisolone Sodium Succinate for Injection may result in dermal and/or subdermal changes forming depressions in the skin at the injection site. In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

7.1 Special Populations

7.1.1 Pregnant Women

Corticosteroids readily cross the placenta. Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Administration of corticosteroids to pregnant animals can cause fetal malformations (cleft palate, skeletal malformations) and intra-uterine growth retardation (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity).

One retrospective study found an increased incidence of low birth weights in infants born to mothers receiving corticosteroids. Cataracts have been observed in infants born to mothers undergoing long-term treatment with corticosteroids during pregnancy.

Since adequate human reproductive studies have not been done with methylprednisolone sodium succinate, Methylprednisolone Sodium Succinate for Injection should be used during pregnancy only at the lowest possible dose, only if clearly needed, where the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Infants born to mothers who received substantial doses of corticosteroids during pregnancy should be observed for signs of hypoadrenalism and appropriate measures instituted if such signs are present. There are no known effects of corticosteroids on labour and delivery.

Benzyl alcohol can be introduced into the solution when Methylprednisolone Sodium Succinate for Injection vials are reconstituted with Bacteriostatic Water for Injection USP (benzyl alcohol as preservative) as directed. Benzyl alcohol can cross the placenta.

7.1.2 Breast-feeding

Corticosteroids are excreted in breast milk. Corticosteroids distributed into breast milk may suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a careful benefit-risk assessment should be conducted and a decision should be made whether to discontinue nursing, or discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Methylprednisolone Sodium Succinate for Injection is contraindicated for use in premature infants (see 2 CONTRAINDICATIONS). Benzyl alcohol can be introduced into the solution when Methylprednisolone Sodium Succinate for Injection vials are reconstituted with Bacteriostatic Water for Injection USP (benzyl alcohol as preservative). Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients, including the “gasping syndrome” in neonate and low-birth weight infants. The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine. Additional symptoms may

include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants, as well as patients receiving high doses (>90 mg/kg/day), may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Pediatric patients may experience a decrease in their growth velocity at low systemic doses and in the absence of laboratory evidence of HPA axis suppression. Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis.

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

High doses of corticosteroids may produce pancreatitis in children.

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

7.1.4 Geriatrics

See section 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations, Geriatrics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following Adverse Reactions have been reported with the systemic use of methylprednisolone sodium succinate and other corticosteroid preparations.

MedDRA (v15) System Organ Class	Undesirable Effect

Blood and lymphatic system disorders	Leukocytosis
Infections and infestations	Infection; opportunistic infection; injection site infections following non-sterile administration; decreased resistance to infection
Immune system disorders	Drug hypersensitivity; (anaphylactoid reaction; anaphylactic reaction (with or without circulatory collapse))
Endocrine disorders	Cushingoid; hypopituitarism; steroid withdrawal syndrome; moon face; abnormal fat deposits; glycosuria; hypertrichosis; secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness) 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.
Metabolism and nutrition disorders	Lipomatosis; sodium retention; sodium excretion; fluid retention; alkalosis hypokalemic; dyslipidaemia; metabolic acidosis; glucose tolerance impaired; increased requirement for insulin (or oral hypoglycemic agents in diabetics); nitrogen balance negative (due to protein catabolism); blood urea increased; increased appetite (which may result in weight increased); diuresis
Psychiatric disorders	Affective disorder (including affect lability, depressed mood, euphoric mood, drug dependence, suicidal ideation); psychotic disorder (including mania, delusion, hallucination, schizophrenia [aggravation of]); mental disorder; insomnia; mood swings; personality change; confusional state; abnormal behavior; anxiety; irritability; emotional instability
Nervous system disorders	Epidural lipomatosis; intracranial pressure increased (with papilloedema [idiopathic intracranial hypertension] usually following discontinuation of treatment); convulsion; amnesia; cognitive disorder; dizziness; headache; seizures; neuritis; neuropaty; paresthesia
Eye disorders	Central serous chorioretinopathy; cataract; glaucoma; exophthalmos; rare instances of blindness associated with periocular injections.
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Cardiac failure congestive (in susceptible patients); arrhythmia; cardiac arrest; bradycardia; tachycardia; cardiac enlargement; circulatory collapse; hypertrophic cardiomyopathy in premature infants; myocardial rupture following recent myocardial infarction; pulmonary oedema; syncope
Vascular disorders	Hypertension; hypotension; thromboembolism; thrombophlebitis, thrombosis, vasculitis
Respiratory, thoracic and mediastinal disorders	Hiccups; bronchospasm, pulmonary embolism
Gastrointestinal disorders	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage); intestinal perforation; gastric haemorrhage; pancreatitis; esophagitis ulcerative; oesophagitis; abdominal distension; abdominal pain; diarrhoea; dyspepsia; nausea; vomiting; dysgeusia; peritonitis (peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis)
Hepatic disorders	Hepatomegaly, hepatitis, drug-induced liver injury , liver failure

Skin and subcutaneous disorders	Angioedema; hirsutism; petechiae; ecchymoses; skin atrophy; erythema; hyperhidrosis; skin striae; rash; pruritus; urticaria; acne; skin hypopigmentation; skin hyperpigmentation; allergic dermatitis; burning or tingling (especially in the perineal area after intravenous injection); cutaneous and subcutaneous atrophy; dry scaly skin; sterile abscess; thinning scalp hair; Kaposi's sarcoma
Musculoskeletal and connective tissue disorders	Muscular weakness; myalgia; myopathy; muscle atrophy; osteoporosis; osteonecrosis; pathological; fracture; neuropathic arthropathy; arthralgia; growth retardation
Reproductive system and breast disorders	Menstruation irregular; increased or decreased motility and number of spermatozoa.
General disorders and administration site conditions	Impaired healing; fatigue; malaise; injection site reaction; oedema peripheral
Investigations	Urine calcium increased; blood potassium decreased; Carbohydrate tolerance decreased; intraocular pressure increased; aminotransferase increased; aspartate aminotransferase increased; blood alkaline phosphatase increased; suppression of reactions to skin tests; post-injection flare (following intra-articular use); blood urea increased
Injury, poisoning and procedural complications	Spinal compression fracture; tendon rupture (particularly of the Achilles tendon)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A 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 affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration.

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

9.4 Drug-Drug Interactions

The following table provides a list of drugs that may interact with methylprednisolone.

CLASS OF DRUG	DRUG(S) INVOLVED	CLINICAL IMPLICATION	MECHANISM
Antibiotics/ Antifungals	Troleandomycin *(not marketed in Canada)* Erythromycin Ketoconazole Itraconazole	Enhanced clinical effects and side effects of methylprednisolone.	Enzyme inhibition: Reduced MP elimination.
	Isoniazid	There is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid	CYP3A4 Inhibitor
	Rifampin	May reduce efficacy; dosage adjustment may be required.	Enzyme induction, increased clearance.
	Clarithromycin Erythromycin		CYP3A4 Inhibitor (and Substrate)
Anticholinergics	Pancuronium	Partial reversal of neuromuscular block.	

CLASS OF DRUG	DRUG(S) INVOLVED	CLINICAL IMPLICATION	MECHANISM
	Neuromuscular blockers	1) An Acute myopathy has been reported with concomitant high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. 2) Antagonism of the neuromuscular blocking effects of pancurinium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.	
Anticholinesterases	Neostigmine, Pyridostigmine Steroids	Precipitation of myasthenic crisis. Anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy. Steroids may reduce the effects of anticholinesterases in myasthenia gravis.	
Anticoagulants	Oral Anticoagulants or Heparin	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	

CLASS OF DRUG	DRUG(S) INVOLVED	CLINICAL IMPLICATION	MECHANISM
	Warfarin	effects. Inhibition of response to warfarin. Coagulation indices should be monitored frequently to maintain desired anticoagulant effect.	
Anticonvulsants	e.g. Phenobarbital Phenytoin Carbamazepine	May reduce methylprednisolone efficacy. Monitor clinical response. Adjust dose if necessary.	Enzyme induction: increased clearance of methylprednisolone
Antidiabetics	e.g. Insulin, Glibenclamide, Metformin	Because corticosteroids may increase corticosteroid concentrations, dosage adjustments of antidiabetic agents may be required.	Diabetogenic effects of corticosteroid.
Antiemetics	Aprepitant Fosaprepitant		CYP3A4 Inhibitor
Antihyper-Cholesterolemics and Antidiarrheals	Cholestyramine	May increase the clearance of corticosteroids.	
Antihypertensive Agents	All Antihypertensives	May result in partial loss of hypertensive control.	Mineralocorticoid effect of corticosteroid leading to raised blood pressure.
Antitubercular Drugs	Isoniazid	Serum concentrations of isoniazid may be decreased.	
Antivirals	HIV-Protease inhibitors	Protease inhibitors, such as indinavir and ritonavir, may increase plasma levels of corticosteroids. Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.	CYP3A4 Inhibitor (and Substrate)
Aromatase Inhibitors	Aminoglutethimide *(not marketed in Canada)*	May lead to a loss of corticosteroid-induced adrenal suppression.	

CLASS OF DRUG	DRUG(S) INVOLVED	CLINICAL IMPLICATION	MECHANISM
		Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.	
Cardioactive Drugs	Digoxin and related Glycosides Calcium Channel Blockers e.g. Diltiazem	Potentiation of digoxin toxicity. Increased risk of arrhythmias due to hypokalemia.	Corticosteroid induced potassium loss (mineralocorticoid effect) CYP3A4 Inhibitor and Substrate)
Potassium-Depleting Agents	All potassium losing diuretics e.g. Furosemide Amphotericin B Xanthenes Beta$_2$ agonists	Enhanced toxicity. Monitor K+ levels and supplement if necessary. Development of hypokalemia. When corticosteroids are administered concomitantly with potassium-depleting agents (i.e. diuretics), patients should be observed closely for development of hypokalemia. There is also and an increased risk for hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists.	Potassium loss.
Estrogens, Including Oral Contraceptives	Ethinylestradiol/ Norethindrone	May decrease hepatic metabolism of certain corticosteroids, thereby increasing their effect.	CYP3A4 Inhibitor
Immunizing Agents	Live Vaccine:	May see increased toxicity	Corticosteroid

CLASS OF DRUG	DRUG(S) INVOLVED	CLINICAL IMPLICATION	MECHANISM
	Poliomyelitis, BCG, Mumps, Measles, Rubella, Smallpox Killed Virulent Vaccines	from vaccine. Disseminated viral disease may occur. Reduced response to vaccine.	induced immunosuppression Impaired immune response.
Immuno-suppressants	Methotrexate Azathioprine Cyclosporine (CYA)	May allow reduced dose of corticosteroid. 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon coadministration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine.	Synergistic effect on disease state. CYP3A4 Inhibitor (and Substrate)
	Cyclophosphamide Tacrolimus		CYP34A Substrate
Psychotherapeutic	Anxiolytics Antipsychotics	Recurrence or poor control of CNS symptoms. May require dose adjustment.	CNS effects of corticosteroid.
Nonsteroidal Anti-inflammatory Agents (NSAIDs)	e.g. Aspirin	1) Concomitant use of nonsteroidal anti-inflammatory agents and corticosteroids increases risk	Increased clearance and decreased plasma level.

CLASS OF DRUG	DRUG(S) INVOLVED	CLINICAL IMPLICATION	MECHANISM
		of gastrointestinal side effects. 2) Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. 3) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 4) Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.	CYP34A Inhibitor
Sympathomimetic Agents	e.g. Salbutamol	Increased efficacy and potentially increased toxicity.	Increased response to sympathetic agents.

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, calcium gluconate, vencuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol (see also 4 DOSAGE AND ADMINISTRATION, Compatibility).

9.5 Drug-Food Interactions

Interactions with food have not been established.

Grapefruit juice is a CYP3A4 inhibitor. See 9 DRUG INTERACTIONS, CYP3A4 INHIBITORS above.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Corticosteroids may suppress reactions to skin tests.

10 CLINICAL PHARMACOLOGY

10.2 Pharmacodynamics

Methylprednisolone is a potent anti-inflammatory steroid.

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, following intravenous administration, is at least four to one. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.

The metabolism and excretion of methylprednisolone sodium succinate is similar to that of other corticosteroids. It influences carbohydrate, protein, fat and purine metabolism, electrolyte and water balance, and the functional capacities of the cardiovascular system, the kidney, skeletal muscle, the nervous system and other organs and tissues.

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.

COMPOUND	DOSE	HALF-LIFE (minutes)
Methylprednisolone	25 mg	188
Prednisolone	25 mg	69
Hydrocortisone	25 mg	57

10.3 Pharmacokinetics

Methylprednisolone pharmacokinetics are linear, independent of the route of administration.

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

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 bioequivalent and significantly greater than those following administration of the oral solution and oral methylprednisolone tablets. Since the extent of methylprednisolone absorbed following the IV and IM treatment was equivalent, in spite of the greater amount of the hemisuccinate ester reaching the general circulation after IV administration, it appears that the ester is converted in the tissue after IM injection, with subsequent absorption as free methylprednisolone.

Distribution:
Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier and is secreted in breast milk. Its apparent volume of distribution is approximately 1.4 L/kg. The plasma protein binding of methylprednisolone in humans is approximately 77%.

Metabolism:
In humans, methylprednisolone is metabolized in the liver to inactive metabolites, primarily 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4 (see 9 DRUG INTERACTIONS).

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

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

11 STORAGE, STABILITY AND DISPOSAL

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 programs, 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, and 1 g vials, reconstituted as indicated in the Reconstitution Table, should be used within 48 hours. **Discard unused solution**.

Keep in a safe place out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

This information is not available for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

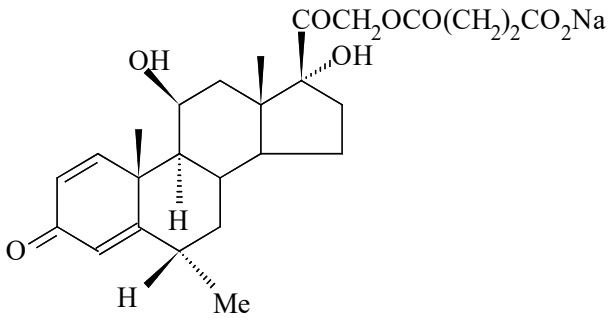
Drug Substance

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, (6α,11β)

Molecular formula and molecular weight: $C_{26}H_{33}NaO_8$, 496.53 g/mol

Structural Formula:



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.

14 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 methyl prednisolone 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicology:
The acute LD_{50} of methylprednisolone sodium succinate intraperitoneally in the mouse is 850 mg/kg. The oral LD_{50} 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:
Methylprednisolone has not been evaluated in rodent carcinogenicity studies.

Variable results have been obtained with other glucocorticoids tested for carcinogenicity in mice and rats. However, published data indicate that several related glucocorticoids including budesonide, prednisolone, and triamcinolone acetonide can increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water to male rats. These tumorigenic effects occurred at doses which were less than the typical clinical doses on a mg/m^2 basis.

Mutagenesis:
Methylprednisolone has not been evaluated for genotoxicity.

However, methylprednisolone sulfonate, which is structurally similar to methylprednisolone sodium succinate, was not mutagenic with or without metabolic activation in Salmonella typhimurium, or in a mammalian cell gene mutation assay using Chinese hamster ovary cells. Methylprednisolone suleptanate did not induce unscheduled DNA synthesis in primary rat hepatocytes. Moreover, a review of published data indicates that prednisolone farnesylate (PNF), which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in Salmonella typhimurium and Escherichia coli strains. In a Chinese

hamster fibroblast cell line, PNF produced a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested.

Reproductive and Developmental Toxicity:
Corticosteroids have been shown to reduce fertility when administered to rats. Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced in untreated females mated with males treated at the administered doses of 10 and 25 mg/kg/day.

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. SOLU-MEDROL® Sterile Powder, 500 mg, 1 g Vials, Submission Control No. 255703, Product Monograph, Pfizer Canada ULC. (FEB 07, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]methylPREDNISolone SODIUM SUCCINATE FOR INJECTION

Methylprednisolone Sodium Succinate for Injection

Read this carefully before you start taking **Methylprednisolone Sodium Succinate for Injection** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Methylprednisolone Sodium Succinate for Injection**.

What is methylPREDNISolone SODIUM SUCCINATE FOR INJECTION used for?
- Methylprednisolone Sodium Succinate for Injection is used in adults and children to treat many conditions. These include allergic reactions and inflammation.

What does methylPREDNISolone SODIUM SUCCINATE FOR INJECTION work?
Methylprednisolone Sodium Succinate for Injection is a synthetic corticosteroid. It decreases the body's reaction to some severe conditions and reduces inflammation.

What are the ingredients in methylPREDNISolone SODIUM SUCCINATE FOR INJECTION?
Medicinal ingredients: methylprednisolone sodium succinate

Non-medicinal ingredients: dibasic sodium phosphate dried and monobasic sodium phosphate anhydrous. When needed, the pH is adjusted with sodium hydroxide. The 40mg strength also contains lactose produced from cow's milk.

methylPREDNISolone SODIUM SUCCINATE FOR INJECTION comes in the following dosage forms:
Methylprednisolone Sodium Succinate for Injection comes in vials containing sterile powder.
The available formulations are:
- 40 mg per vial
- 125 mg per vial
- 500 mg per vial
- 1 g per vial

Do not use methylPREDNISolone SODIUM SUCCINATE FOR INJECTION if:
- you are allergic to methylprednisolone sodium succinate or any ingredient of this medication.
- you are lactose intolerant. 40mg strength contains lactose
- you have a fungal infection or any untreated infection
- you have recently received a type of vaccine called a live or live / attenuated vaccine. Do not receive this vaccine during treatment with Methylprednisolone Sodium Succinate for Injection.
- you have a blood condition called idiopathic thrombocytopenic purpura (low platelet count), for intramuscular use.

Methylprednisolone Sodium Succinate for Injection should not be used in premature and low-birth infants. The diluent contains benzyl alcohol, which can cause serious side effects and death.

This medicine is not injection via the spinal cord or brain (intrathecal or epidural).

Except for short-term or emergency use such as severe allergic reactions, do not use Methylprednisolone Sodium Succinate for Injection if you have:

- viral diseases including vaccinia (cowpox), varicella (chickenpox), and herpes simplex of the eye
- a serious lung infection (tuberculosis)
- a serious mental disorder (psychoses)
- Cushing's syndrome (a condition caused by excess corticosteroids)
- a stomach ulcer
- kidney problems

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take methylPREDNISolone SODIUM SUCCINATE FOR INJECTION. Talk about any health conditions or problems you may have, including if you:

- have an infection (such as herpes simplex, chicken pox, tuberculosis, threadworm); **If you or your child is exposed to measles or chickenpox during treatment with Methylprednisolone Sodium Succinate for Injection, contact your healthcare professional immediately. Serious or fatal side effects can occur if you or your child have not already had these infections.**
- have recently had or are about to have any vaccine
- recently had heart problems such as a heart attack, heart failure or heart disease
- have bleeding or blood clotting problems
- have brittle bone (osteoporosis)
- have high blood pressure
- have water retention (oedema)
- have or had seizures or other nervous system problems
- have thyroid problems
- have muscle pain or muscle weakness (such as myasthenia gravis)
- have a tumor of the adrenal glands (pheochromocytoma)
- have certain eye diseases such as glaucoma, cataracts, herpes infection or any problems with the retina
- have a condition known as systemic sclerosis, in which your body makes too much of a protein called collagen.
- have kidney disease
- have liver disease such as cirrhosis
- have diabetes (high blood sugar)
- have certain mental or mood conditions (such as depression)
- have stomach or gut problems (ulcer, ulcerative colitis)
- have low potassium or calcium
- have Cushing's disease (caused by an excess of cortisol hormone)
- have a weak immune response. Tell your healthcare professional if you suspect an infection has occurred, as corticosteroids can make infections more likely and may mask their signs
- had any prior use of Methylprednisolone Sodium Succinate for Injection.

Other warnings you should know about:

Serious Side Effects: Methylprednisolone Sodium Succinate for Injection can cause serious side effects, including:

- skin cancer (Kaposi's sarcoma): Kaposi's sarcoma has been reported with corticosteroid therapy, such as Methylprednisolone Sodium Succinate for Injection. Stopping treatment of Methylprednisolone Sodium Succinate for Injection may result in signs of this cancer going away.
- tumor of the adrenal glands (pheochromocytoma). This tumor has been reported with corticosteroid therapy, such as Methylprednisolone Sodium Succinate for Injection. Pheochromocytoma may cause death.
- fat deposition on or outside the lining of the spine (epidural lipomatosis). Taking corticosteroids in high doses for a long period of time can cause epidural lipomatosis.

Surgery: Before you have any operation, tell your doctor, dentist or anesthetist that you are taking Methylprednisolone Sodium Succinate for Injection.

Pregnancy and breastfeeding:

- If you are pregnant, or still able to get pregnant and/or breast-feed, there are specific risks you must discuss with your healthcare professional. Taking Methylprednisolone Sodium Succinate for Injection may:
    - slow the growth and cause low birth weight of the baby.
    - cause cataracts in babies. This risk is associated with mothers who take corticosteroids for a long period of time during pregnancy.
- If you are breastfeeding or planning to breastfeed, tell your healthcare professional.

Male fertility: Taking Methylprednisolone Sodium Succinate for Injection may affect male fertility.

Stopping treatment: If you suddenly stop taking Methylprednisolone Sodium Succinate for Injection, you may experience:

- Serious adrenal insufficiency. Adrenal insufficiency is when the body does not make enough of the cortisol hormone. This may cause death.
- "Withdrawal syndrome". This includes symptoms such as anorexia, nausea, vomiting, lack of energy, headache, fever, joint pain, peeling of skin, muscle pain, weight loss, and/or low blood pressure

Skin:

- Dents/holes may appear at the site of injection.
- Tell your healthcare professional you are taking Methylprednisolone Sodium Succinate for Injection since it can affect the results of skin tests.

Driving and Using Machines: Methylprednisolone Sodium Succinate for Injection may cause dizziness, vertigo, vision problems and fatigue. If you experience these side effects you should not drive or operate machinery.

Children (less than 18 years of age):

- Children may experience a decrease in the speed of their growth. The healthcare provider will prescribe the lowest dose to minimize this risk.
- The healthcare professional will conduct frequent tests on the child if they are taking Methylprednisolone Sodium Succinate for Injection for a long period of time. Taking hydrocortisone for a long period of time increases the risk of developing a high intracranial pressure (growing pressure in skull).
- If hydrocortisone is given to a prematurely born baby, monitoring of the heart may be needed.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with methylPREDNISolone SODIUM SUCCINATE FOR INJECTION:

- Medicines used to:
    - treat cancer such as cyclophosphamide
    - prevent or relieve a sudden worsening of shortness of breath and wheezing (Beta2 agonists such as salbutamol, budesonide and salmeterol)
    - treat bacterial and fungal infections (antibiotics/antifungals such as rifampin, itraconazole, clarithromycin, ketoconazole, troleandomycin*, erythromycin and amphotericin B)
    - prevent the elimination of a neurotransmitter, acetylcholine (such as neostigmine and pyridostigmine)
    - prevent blood clotting (such as warfarin or heparin)

- treat epilepsy (such as phenobarbital, phenytoin or carbamazepine)
- treat diabetes (such as insulin, glibenclamide or metformin)
- treat high blood pressure (such as amlodipine or quinapril)
- prevent nausea and vomiting associated with cancer chemotherapy treatment (such as aprepitant or fosaprepitant)
- treat high cholesterol (such as cholestyramine)
- treat tuberculosis (such as isoniazid)
- treat HIV infections
- treat Cushing's syndrome, breast or ovarian cancer (aromatase inhibitors such as aminoglutethimide*)
- treat heart problems (such as digoxin, calcium channel blockers)
- reduce extra fluid in the body (diuretics such as furosemide)
- help prevent organ rejection such as cyclosporine or tacrolimus
- to treat inflammatory diseases (including rheumatoid arthritis) such as azathioprine or methotrexate
- treat anxiety or mental health disorders/mental illnesses (like diazepam or clozapine)
- treat diarrhea

*not marketed in Canada

- Vaccines
- Neuromuscular Blocking Agents (agents that block signals between nerves and muscles such as pancuronium)
- Aspirin and non-steroidal anti-inflammatory medicines (also called NSAIDs) such as ibuprofen
- Sympathomimetic Agents (agents that mimic the effects of adrenaline like salbutamol, used to treat asthma)
- Hormone replacement therapy or hormonal oral birth control

Do not drink grapefruit juice while taking Methylprednisolone Sodium Succinate for Injection.

How to take methylPREDNISolone SODIUM SUCCINATE FOR INJECTION:

- Methylprednisolone Sodium Succinate for Injection will be given to you by your healthcare professional. They will decide to give Methylprednisolone Sodium Succinate for Injection to you by either:
  - Infusion into your vein (intravenous infusion) over 1 hour; or
  - Slow injection into your vein (intravenous injection); or
  - Injection into your muscle (intramuscular).
- Your healthcare professional will decide on the site of injection, as well as how much of the medicine and how many injections you will receive.
- The healthcare professional will prescribe the lowest possible dose for the minimum period of time.

Usual dose:

- The dose you will receive depends on the:
  - type of condition being treated;
  - severity of the condition;
  - your response to the treatment, and
  - your exposure to physical stress like infection, surgery or injury.

Overdose:

If you think you, or a person you are caring for, have taken too much Methylprednisolone Sodium Succinate for Injection, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using methylPREDNISolone SODIUM SUCCINATE FOR INJECTION?

These are not all the possible side effects you may have when taking Methylprednisolone Sodium Succinate for Injection. If you experience any side effects not listed here, tell your healthcare professional.

Infections:
Methylprednisolone Sodium Succinate for Injection may:

- hide symptoms of infections
- reactivate dormant infections
- induce infections due to lowered body resistance

Heart problems:

- Low blood pressure
- Fainting
- Blood clots
- Thrombophlebitis (vein inflammation)
- Pediatric hypertrophic cardiomyopathy (thickening of heart muscle)

Skin problems:

- Ecchymoses (spots caused by ruptured blood vessels)
- Petechiae (reddish spot containing blood that appears in skin)
- Acne
- Rash, redness, itchy skin
- Dry scaly skin
- Increased sweating
- Lightening or darkening of an area of the skin
- Abscess
- Thinning scalp hair
- Injection site infections/reactions: blistering, pain, skin changes/depressions, tenderness, warmth in the area around the injection

Endocrine and metabolism problems:

- Development of Cushingoid state (abnormal bodily condition caused by excess corticosteroids)
- Moon face (enlargement of face and forehead)
- Weight gain
- Abnormal fat deposits
- hypopituitarism (a condition in which your pituitary gland fails to produce one or more of its hormones or does not produce enough of them).
- 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
- Sodium retention and excretion
- Increased urination
- Decreased carbohydrate (sugar) tolerance
- New symptoms of diabetes, need for higher doses of insulin or sugar lowering pills in diabetics

Gastrointestinal problems:

- Stomach ulcer or bleeding
- Inflammation of the pancreas, esophagus, peritoneum
- Perforation of the bowel
- Nausea, vomiting, diarrhea
- Altered sense of taste (with rapid administration of large doses)
- Abdominal pain, bloating
- Bowel/bladder dysfunction
- Increased or decreased appetite

Liver problems:

- Enlarged liver
- Liver injury
- Hepatitis (liver inflammation)

Musculoskeletal problems:

- Muscle disease
- Muscle pain
- Loss of muscle mass
- Malaise (feeling of general discomfort or uneasiness)
- Aseptic necrosis (tissue death)
- Fractures caused by disease, spine fractures
- Tendon rupture, particularly of the Achilles tendon
- Charcot joint disease (foot and ankle problems)

Nervous system problems:

- Increased pressure within the skull with oedema and inflammation of the optic nerve
- Headache
- Pain and tenderness
- Impaired sensation, strength and reflexes
- Sensation of tingling, tickling, prickling or burning of a person's skin
- Vertigo, dizziness
- Meningitis (inflammation of membranes that surround brain and spinal cord)
- Amnesia

Eye problems:

- Protrusion of the eyeball
- Blindness

Psychiatric problems:

- Emotional instability
- Euphoria (intense feelings of well-being, elation, happiness, excitement, and joy)
- Personality changes
- Delusion
- Hallucination
- Confusion
- Schizophrenia
- Irritability

Sexual Function/Reproduction:

- Irregular periods
- Increased or decreased mobility and number of sperm

Blood problems:

- Above normal white blood cell count
- Above normal cholesterol or triglycerides/blood fats
- Abnormal blood tests (ex. liver enzymes and urea)

Other:

- Hiccups
- Fatigue

Serious side effects and what to do about them		
Symptom / effect	**Talk with your healthcare professional**	**Stop taking drug and get immediate medical help**

	Only if severe	In all cases	
UNKNOWN			
Convulsion: seizure, shaking or fits			✓
Cramps and spasms		✓	
Diabetes: Increased thirst/urination		✓	
Easy bruising/bleeding			✓
Edema: Fluid retention, swelling		✓	
Eye problems: failing eyesight, blurry vision, eye pain, increased pressure in your eyes		✓	
Epidural lipomatosis (fat buildup on outside of spine): back pain, weakness, loss of sensation or reflexes that are to slow or too fast			✓
Flare up of a previous Tuberculosis: symptoms of which could be coughing blood or pain in the chest			✓
Heart failure: Shortness of breath, fatigue, weakness, dizziness, irregular or fast pounding heart beat			✓
High blood pressure: headaches or generally feeling unwell		✓	
Hormonal changes: Irregular menstrual periods, unusual hair growth	✓		
Kaposi's sarcoma (a type of skin cancer): slightly elevated purple, pink, brown, black, blue, or red blotches or bumps anywhere on the skin or in the mouth and/or throat			✓
Mental problems: mood swings, depression, suicidal thinking, agitation, anxiety, trouble sleeping		✓	
Muscle weakness			✓
Osteoporosis (thin, fragile bones): broken bones, bone pain, back pain that gets worse when standing **or** walking			✓
Pheochromocytoma (adrenal gland tumour): symptoms often include high blood pressure, sweating, rapid heartbeat, and headache			✓
Serious allergic reaction: symptoms of which include rash, itching/swelling (especially of the face/tongue/throat), severe dizziness and trouble breathing			✓
Signs of infection: persistent fever/cough/sore throat, painful urination, eye pain/discharge		✓	
Stomach ulcers (burst or bleeding ulcers): symptoms of which are stomach pain, bleeding from the rectum, black or bloodstained stools and/or vomiting blood			✓
Tendon pain or joint pain			✓
Thinning skin	✓		
Wounds that are slow to heal	✓		

Unusual skin growth (nodules or blotches that may be red, purple, brown or black and may be raised)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Before Reconstitution: Store Methylprednisolone Sodium Succinate for Injection 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.

If you want more information about methylPREDNISolone SODIUM SUCCINATE FOR INJECTION:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html ; the manufacturer's website http://www.tevacanada.com ; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com .

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario, M1B 2K9.

Last Revised: September 23, 2022