

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SOLU-MEDROL® 1 g powder for injection

SOLU-MEDROL® 2 g powder for injection*

SOLU-MEDROL® ACT-O-VIAL 40 mg/mL powder for injection

SOLU-MEDROL® ACT-O-VIAL 125 mg/2 mL powder for injection

SOLU-MEDROL® ACT-O-VIAL 500 mg/4 mL injection with diluent

*Not available.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SOLU-MEDROL 1 g powder for injection

Each vial with active constituent contains methylprednisolone sodium succinate equivalent to methylprednisolone 1 g.

Excipients with known effect

Each vial of diluent contains benzyl alcohol 140.4 mg as preservative.

When mixed as directed, each 16 mL contains methylprednisolone sodium succinate equivalent to methylprednisolone 1 g.

SOLU-MEDROL 2 g powder for injection

Each vial with active constituent contains methylprednisolone sodium succinate equivalent to methylprednisolone 2 g.

Excipients with known effect

Each vial of diluent contains benzyl alcohol 280.8 mg as preservative.

When mixed as directed, each 31.2 mL contains methylprednisolone sodium succinate equivalent to methylprednisolone 2 g.

SOLU-MEDROL ACT-O-VIAL 40 mg/mL powder for injection

The vial compartment with the active constituent contains methylprednisolone sodium succinate equivalent to methylprednisolone 40 mg.

When mixed, each mL contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone.

SOLU-MEDROL ACT-O-VIAL 125 mg/2 mL powder for injection

The vial compartment with the active constituent contains methylprednisolone sodium succinate equivalent to methylprednisolone 125 mg.

When mixed, each 2 mL contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone.

SOLU-MEDROL ACT-O-VIAL 500 mg/4 mL

The vial compartment with the active constituent contains methylprednisolone sodium succinate equivalent to methylprednisolone 575 mg.

When mixed each 4 mL contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

SOLU-MEDROL:

- powder for injection: white, freeze-dried cake
- diluent: clear, colourless liquid.

SOLU-MEDROL ACT-O-VIAL:

- powder for injection: white, freeze-dried cake
- diluent: clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Endocrine Disorders

- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogues may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).
- Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogues are used).
- Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.
- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis
- Hypercalcaemia associated with cancer.

Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- Post-traumatic osteoarthritis
- Synovitis of osteoarthritis

- Rheumatoid arthritis including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Acute and subacute bursitis
- Epicondylitis
- Acute non-specific tenosynovitis
- Acute gouty arthritis
- Psoriatic arthritis
- Ankylosing spondylitis.

Collagen Diseases (Immune and Complex Diseases)

During an exacerbation or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus (and lupus nephritis)
- Acute rheumatic carditis
- Systemic dermatomyositis (polymyositis)
- Polyarteritis nodosa
- Good pasture's syndrome.

Dermatologic Diseases

- Pemphigus
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Exfoliative dermatitis
- Bullous dermatitis herpetiformis
- Severe seborrhoeic dermatitis
- Severe psoriasis
- Mycosis fungoides.

Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

- Bronchial asthma
- Contact dermatitis
- Atopic dermatitis
- Serum sickness
- Drug hypersensitivity reactions
- Urticarial transfusion reactions
- Acute non-infectious laryngeal oedema (adrenaline is the drug of first choice).

Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

- Herpes zoster ophthalmicus
- Iritis, iridocyclitis
- Chorioretinitis
- Diffuse posterior uveitis and choroiditis
- Optic neuritis
- Sympathetic ophthalmia
- Anterior segment inflammation
- Allergic conjunctivitis
- Allergic corneal marginal ulcers
- Keratitis.

Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:

- Ulcerative colitis (systemic therapy)
- Regional enteritis (systemic therapy).

Respiratory Diseases

- Symptomatic sarcoidosis
- Berylliosis
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate anti-tuberculous chemotherapy
- Loeffler's Syndrome not manageable by other means
- Aspiration pneumonitis

SOLU-MEDROL is beneficial as adjunctive therapy in the treatment of AIDS patients with moderate to severe *pneumocystis jiroveci* pneumonia when given in the first 72 hours of initial anti-pneumocystis treatment. Due to the increased rate of reactivation of tuberculosis in AIDS patients, consideration should be given to the administration of antimycobacterial therapy if corticosteroids are used in this high risk group. The patient should also be observed for activation of other latent infections.

Haematologic Disorders

- Acquired (autoimmune) haemolytic anaemia
- Idiopathic thrombocytopenia purpura in adults (IV only; IM administration is contraindicated)
- Secondary thrombocytopenia in adults
- Erythroblastopenia (RBC anaemia)

- Congenital (erythroid) hypoplastic anaemia

Neoplastic Diseases

For palliative management of:

- Leukaemias and lymphomas in adults
- Acute leukaemia of childhood

Terminal Cancer

To improve quality of life in patients with terminal cancer.

Oedematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uraemia, of the idiopathic type or that due to lupus erythematosus.

Nervous System

- Cerebral oedema from tumour - primary or metastatic and/or associated with surgical or radiation therapy.
- Acute exacerbations of multiple sclerosis.
- Acute spinal cord injury - the treatment should begin within eight hours of injury.

Cardiovascular Conditions

Shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present (Hydrocortisone is generally the drug of choice. When mineralocorticoid activity is undesirable, methylprednisolone may be preferred).

Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
- Trichinosis with neurologic or myocardial involvement.
- Organ transplantation.
- Prevention of nausea and vomiting associated with cancer chemotherapy.

4.2 Dose and method of administration

Dose

WARNING - SOME SOLU-MEDROL FORMULATIONS CONTAIN BENZYL ALCOHOL. BENZYL ALCOHOL (AS CONTAINED IN THE ACCOMPANYING DILUENT FOR THE 1 G AND 2 G VIALS) HAS BEEN REPORTED TO BE ASSOCIATED WITH A FATAL “GASPING SYNDROME” IN PREMATURE INFANTS (SEE SECTION 2 AND SECTION 4.4, PAEDIATRIC USE).

Because of possible physical incompatibilities, SOLU-MEDROL should not be diluted or mixed with other solutions.

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 (see **section 4.4**).

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 (see **section 4.4**).

Use only the accompanying diluent (bacteriostatic Water for Injections with benzyl alcohol or the sterile Water for Injection when reconstituting SOLU-MEDROL) (see **section 4.2, Preparation of solutions**).

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

SOLU-MEDROL (methylprednisolone sodium succinate) may be administered by intravenous or intra-muscular injection, or by intravenous infusion, the preferred method for initial emergency use being intravenous injection. To administer by intravenous (or intramuscular) injection, prepare solution with the diluent provided. Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

There are reports of cardiac arrhythmias and/or cardiac arrest following the rapid administration of large IV doses of SOLU-MEDROL (**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.

As adjunctive therapy in life-threatening conditions, the recommended dose of SOLU-MEDROL sterile powder is 30 mg/kg of methylprednisolone sodium succinate, given IV over a period of at least 30 minutes. This dose may be repeated every 4-6 hours for up to 48 hours.

Pulse dosing for corticosteroid responsive diseases in exacerbation and/or unresponsive to standard therapy (e.g., lupus nephritis, rheumatoid arthritis, etc.). Suggested schedules:

Rheumatic disorders

1 g/day for one, two, three or four days IV or 1 g/month for six months IV.

Systemic lupus erythematosus

1 g/day for three days IV.

Multiple sclerosis

Administer 500 mg/day or 1 g/day for 3 or 5 days as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates.

Oedematous states e.g., glomerulonephritis, lupus nephritis

30 mg/kg every other day for four days IV or 1 g/day for three, five or seven days IV.

The regimen should be administered over at least 30 minutes, and may be repeated if improvement has not occurred within a week after therapy or as patient's condition dictates.

Terminal cancer - Quality of life

Prospective controlled studies have shown that SOLU-MEDROL 125 mg administered intravenously daily for up to eight weeks, significantly improves quality of life in patients with terminal cancer.

Prevention of nausea and vomiting associated with cancer chemotherapy. Suggested schedules: Mild to moderately emetogenic chemotherapy: Administer SOLU-MEDROL 250 mg IV over at least five minutes one hour before chemotherapy, at the initiation of chemotherapy, and at the time of discharge.

A chlorinated phenothiazine may also be used with the first dose of SOLU-MEDROL for increased effect.

Severely emetogenic chemotherapy: Administer SOLU-MEDROL 250 mg IV over at least five minutes with appropriate doses of metoclopramide or a butyrophenone one hour before chemotherapy, then SOLU-MEDROL 250 mg IV at the initiation of chemotherapy and at time of discharge.

Acute spinal cord injury - Treatment should begin within 8 hours of injury

For patients initiated on treatment within 3 hours of injury: Administer 30 mg/kg as an IV bolus over a 15-minute period, followed by a 45-minute pause, and then a continuous IV infusion of 5.4 mg/kg/h for 23 hours.

For patients initiated on treatment within 3 to 8 hours of injury: Administer 30 mg/kg as an IV bolus over a 15-minute period, followed by a 45-minute pause, and then a continuous IV infusion of 5.4 mg/kg/h for 47 hours.

There should be a separate intravenous site for the infusion pump. The treatment should begin within eight hours of injury.

Pneumocystis jiroveci pneumonia in patients with AIDS

A number of dosage schedules have been used. One approach is to administer 40mg SOLU-MEDROL every 6 to 12 hours with gradual tapering over a maximum of 21 days or until the end of the pneumocystis therapy. Therapy should be started within 72 hours of initial anti-pneumocystis treatment.

In other indications, initial dosage will vary from 10-500 mg depending on the clinical problem being treated. Larger doses may be required for short-term management of severe, acute conditions. The initial dose, up to 250 mg, should be given intravenously over a period of at least five minutes and if greater than 250 mg, should be given over at least 30 minutes. It should not be less than 0.5 mg/kg every 24 hours. Subsequent doses may be given intravenously or intra-muscularly at intervals dictated by the patient's response and clinical condition. Corticosteroid therapy is an adjunct to, and not a replacement for, conventional therapy.

Use in paediatrics

Dosage may be reduced for infants and children but should be governed more by the severity of the condition and response of the patient than by age or size. It should not be less than 0.5 mg/kg every 24 hours.

Benzyl alcohol has been associated with “gaspings syndrome” in premature infants (see **section 4.4, Paediatric Use**).

Method of Administration

Directions for using the Act-O-Vial system

1. Tap to ensure that the powder is at base of vial and away from the central stopper.
2. Place the Act-O-Vial on a flat, stable surface and hold with one hand.
3. Press down firmly on the plastic activator with the palm of the other hand to force diluent into the lower compartment.
4. Gently mix the solution by turning the vial upside down a number of times. **DO NOT SHAKE THE VIAL.**
5. Remove plastic tab covering centre of stopper.
6. Sterilise top of stopper with an alcohol swab.

Note: Steps 1-6 must be completed before proceeding.

7. Whilst on a flat surface, insert needle **squarely through centre** of stopper until tip is just visible.
8. Invert vial to allow the solution to flow into the top compartment and withdraw the dose.

Preparation of solutions

To prepare solutions for intravenous infusion, first reconstitute SOLU-MEDROL (methylprednisolone sodium succinate) with the diluent provided. This solution may then be added to Glucose Intravenous Infusion 5%, Sodium Chloride Intravenous Infusion 0.9%, Sodium Chloride 0.45% and Glucose 5% Intravenous Infusion or Sodium Chloride 0.9% and Glucose 5% Intravenous Infusion; the resulting admixtures should be used immediately. This solution is for SINGLE USE ONLY. Therapy may be initiated by administering SOLU-MEDROL (methylprednisolone sodium succinate) intravenously over a period of at least five minutes (e.g., doses up to 250 mg) to at least 30 minutes (e.g., doses of 250 mg or more). Parenteral products should be inspected visually for particulate matter and discoloration prior to administration wherever solution and container permit.

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8 and the tonicities are, for the 40 mg per mL solution, 0.50 osmolar; for the 125 mg per 2 mL, 500 mg per 8 mL and 1 g per 16 mL solutions, 0.40 osmolar; for the 2 g per 31.2 mL solutions, 0.42 osmolar (Isotonic saline = 0.28 osmolar).

IMPORTANT - When reconstituting SOLU-MEDROL, use only the accompanying diluent. The diluent with the Act-O-Vial system is sterile Water for Injections and is preservative free. The diluent provided with SOLU-MEDROL 1 g and 2 g is a bacteriostatic Water for Injections containing benzyl alcohol.

4.3 Contraindications

Methylprednisolone sodium succinate is contraindicated:

- in patients who have systemic fungal infections.
- in patients with known hypersensitivity to methylprednisolone or any component of the formulation. The 40 mg Act-O-Vial presentation includes lactose produced from cow's milk. This presentation may contain trace amounts of milk ingredients and is therefore contraindicated in patients with a known or suspected hypersensitivity to cow's milk or its components, or to other dairy products.
- for use by intrathecal, epidural, local injection or any other unspecified route of administration.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see **section 4.4, Immunosuppressive Effects/Increased Susceptibility to Infections**).

4.4 Special warnings and precautions for use

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

Immunosuppressive Effects/Increased Susceptibility to Infections

Due to their suppression of the inflammatory response and immune function, corticosteroids may increase susceptibility to fungal, bacterial and viral infections and their severity. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, they should seek urgent medical attention. Passive immunisation is recommended if non-immune patients who come into contact with chicken pox. If a diagnosis of chicken pox is confirmed the illness warrants specialist care and urgent treatment.

The immunosuppressive effects of corticosteroids may also result in activation of latent infection or exacerbation of existing infection. Corticosteroids should be used with great care in patients with known or suspected parasitic infections such as *Strongyloides* 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 septicaemia.

It is important to note that corticosteroids may increase susceptibility to infection, may mask some signs of infection, which may reach an advanced stage before the infection is recognised, and new infections may appear during their use. There may be decreased resistance and inability to localise 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.

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 immunisation procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

The use of methylprednisolone 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 an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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

SOLU-MEDROL is not recommended for use in patients with septic shock or sepsis syndrome. Recent studies do not establish the efficacy of SOLU-MEDROL in septic shock, and suggest that increased mortality may occur in some subgroups at higher risk (i.e. elevated creatinine greater than 2.0 mg % or secondary infections).

Immune System Effects

Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/anaphylactoid reactions have occurred in patients receiving corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

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

Endocrine Effects

In patients on corticosteroid therapy (or those who have discontinued treatment but continue to experience symptoms of adrenal insufficiency) who are subjected to unusual stress such as intercurrent illness, trauma or surgery, increased dosage (or reinstatement) of rapidly acting corticosteroids may be required.

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

duration of glucocorticoid therapy. This effect may be minimised by use of alternate-day therapy.

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Therefore, withdrawal of corticosteroid should always be gradual.

Symptoms of adrenal insufficiency include: malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

Drug-induced adrenocortical insufficiency may be minimised by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy, therefore, in any situation of stress occurring during that period, hormone therapy should be reinstated.

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

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

Corticosteroids should be used with caution in patients with hypothyroidism as there is potential for an enhanced effect of corticosteroids in these patients.

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

Metabolism and Nutrition

Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes and predisposes those on long term corticosteroid therapy to diabetes mellitus. Therefore, corticosteroids should be used with caution in patients with diabetes mellitus or a family history of diabetes mellitus.

Psychiatric Effects

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Therefore, particular care is required when considering the use of corticosteroids in patients with existing or previous history of severe affective disorders.

Potentially severe psychiatric adverse reactions may occur with systemic corticosteroids (see **section 4.8**). Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

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

Nervous System Effects

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

Corticosteroids should be used with caution in patients with myasthenia gravis (see **section 4.4, Musculoskeletal Effects**).

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see **section 4.2**).

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

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

Ocular Effects

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible risk of corneal scarring, loss of vision and corneal perforation.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

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

Visual Disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Cardiac Effects

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention

should be paid to risk modification and additional cardiac monitoring if needed. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy.

There are reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large IV doses of SOLU-MEDROL (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 (see **section 4.2**, **section 4.8** and **section 4.9**).

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

Vascular Effects

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

Corticosteroids should be used with caution in patients with hypertension.

Gastrointestinal Effects

High doses of corticosteroids may produce acute pancreatitis.

There is no universal agreement on whether corticosteroids *per se* are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

Corticosteroids should be used with caution in non-specific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer, oesophagitis and gastritis.

Hepatobiliary Effects

Drug-induced liver injury such as acute hepatitis can result from cyclical pulsed IV methylprednisolone (usually at doses of 1 g/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.

Musculoskeletal Effects

Corticosteroids should be used with caution in patients with myasthenia gravis who are receiving anticholinesterase therapy as corticosteroid use may decrease plasma anticholinesterase activity.

An acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis) or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalised,

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.

Corticosteroids should be used with caution in patients with osteoporosis. Osteoporosis is a common but infrequently recognised adverse effect associated with a long-term use of large doses of glucocorticoid.

Corticosteroid should be used with caution in patients with Duchenne's muscular dystrophy since transient rhabdomyolysis and myoglobinuria have been reported following strenuous activities.

Corticosteroids should be used with caution in patients with previous steroid myopathy.

Renal and Urinary Disorders

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

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

Investigations

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Discontinuation (see section 4.4, Endocrine Effects)

Injury, Poisoning and Procedural Complications

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

Other

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see **section 4.5, Other Interactions, NSAIDs**).

Paediatric Use

Benzyl alcohol is contained in the accompanying diluent for the 1 g and 2 g vials. The 40 mg Act-O-Vials, 125 mg Act-O-Vials and 500 mg Act-O-Vials do not contain benzyl alcohol. Benzyl alcohol is associated with severe adverse effects, including fatal "gasping syndrome", in paediatric patients. The minimum amount of benzyl alcohol at which toxicity may occur is unknown. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Premature and low-birth-weight infants may be more likely to develop toxicity.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and use of such a regimen should be restricted to the most urgent indications. Alternate-day glucocorticoid therapy usually avoids or minimises this side effect.

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

High doses of corticosteroids may produce pancreatitis in children.

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

Use in the Elderly

The use of corticosteroids, particularly long-term use, in the elderly should be planned bearing in mind the more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

4.5 Interaction with other medicines and other forms of interaction

Methylprednisolone has a wide spectrum of clinical use and is therefore used with numerous concurrent drugs. The interactions summarised below are of known or likely clinical significance. The need for dosage adjustment of either medication will depend on the clinical situation, the dose regimen prescribed and the observed clinical response. The interactions listed have either pharmacokinetic or pharmacodynamic basis.

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is metabolised mainly by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyses 6 β -hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 Inhibitors

Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance, resulting in increased plasma concentration of methylprednisolone. Coadministration of CYP3A4 inhibitors may require titration of methylprednisolone dosage to reduce the risk of adverse effects and avoid steroid toxicity.

CYP3A4 inhibitors include:

- Antifungals such as ketoconazole and itraconazole.
- Antiemetics such as aprepitant and fosaprepitant.
- Immunosuppressants such as ciclosporin. Mutual inhibition of metabolism occurs with concurrent use of ciclosporin 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. Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin.

- Macrolide antibacterials such as clarithromycin, erythromycin and troleandomycin.
- HIV-Protease inhibitors such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. Corticosteroids may induce the metabolism of HIV-protease inhibitors, resulting in reduced plasma concentrations.
- Calcium channel blockers such as diltiazem.
- Isoniazid. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
- Oral contraceptives such as ethinylestradiol and norethisterone, retard the metabolism of corticosteroids due to increased binding to globulin, resulting in increased plasma levels of corticosteroids and potentiating their biological effect. The dose of corticosteroids may need to be adjusted when commencing or stopping oral contraceptive therapy.
- Grapefruit juice.

CYP3A4 Inducers

Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentrations of methylprednisolone. Coadministration of these substances may require an increase in methylprednisolone dosage to achieve the desired result.

CYP3A4 inducers include:

- Anticonvulsants such as phenobarbital, phenytoin, carbamazepine and primidone
- Bactericidal antibiotics such as rifampicin and rifabutin

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. Most CYP3A4 inhibitors are also CYP3A4 substrates.

- Immunosuppressants such as cyclophosphamide and tacrolimus.

Other Interactions

Other interactions and effects that occur with methylprednisolone are described below.

Antidiabetic Agents

Corticosteroids may increase blood glucose levels. Dose adjustments of antidiabetic therapy may be required with concurrent therapy.

Anticholinergics

Corticosteroids may influence the effect of anticholinergics.

Acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see **section 4.4, Musculoskeletal Effects**).

Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.

Anticholinesterases

Steroids may reduce the effects of anticholinesterases in myasthenia gravis.

Anticoagulants (Oral)

The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices (such as INR or prothrombin time) should be monitored to maintain the desired anticoagulant effects.

Aromatase Inhibitors

Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

Cardiac Glycosides

There is a risk of toxicity if hypokalaemia occurs due to corticosteroid treatment.

Diuretics and Other Potassium Depleting Agents

Excessive potassium loss may be experienced with concurrent use of corticosteroids and potassium depleting diuretics (such as frusemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide). Patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists.

Mifepristone

The effect of corticosteroids may be reduced for 3-4 days after taking mifepristone.

NSAIDs

Concomitant administration may increase the risk of gastrointestinal bleeding and ulceration.

Methylprednisolone may increase the renal 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.

Somatropin

Concomitant administration may inhibit the growth promoting effect of somatropin.

Sympathomimetics

There is an increased risk of hypokalaemia with concurrent high doses of corticosteroids and sympathomimetics such as salbutamol, salmeterol, terbutaline or formoterol.

Vaccines

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

4.6 Fertility, pregnancy and lactation

Fertility

Corticosteroids have been shown to impair fertility in animal studies (see **section 5.3, Reproductive Toxicity**).

Pregnancy

Animal studies have shown that corticosteroids, when administered to the mother, may cause fetal malformations. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women. Since adequate human reproductive studies have not been done with methylprednisolone sodium succinate, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Corticosteroids readily cross the placenta. An increased incidence of low-birth weights in infants born of mothers receiving corticosteroids has been reported. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency, although neonatal adrenal insufficiency is rarely reported in infants exposed *in utero* to corticosteroids.

There are no known effects of corticosteroids on labour and delivery.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

Benzyl alcohol can cross the placenta (see **section 4.4, Paediatric Use**).

Lactation

Corticosteroids are excreted in breast milk.

Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

4.7 Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

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

The adverse effects are listed in the table below by system organ class and frequency.

Infections and Infestations

Not known: Opportunistic infection, infection^a, peritonitis^c, oesophageal candidiasis.

Blood and Lymphatic System Disorders

Not known: Leucocytosis.

Immune System Disorders

Not known: Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction.

Endocrine Disorders

Not known: Cushingoid, hypopituitarism, steroid withdrawal syndrome, secondary adrenocortical and pituitary unresponsiveness^b.

Metabolism and Nutrition Disorders

Not known: Metabolic acidosis, sodium retention, fluid retention, alkalosis hypokalaemic, dyslipidaemia, glucose tolerance impaired^c, increased insulin requirement (or oral hypoglycaemic agents in diabetics), lipomatosis, increased appetite (which may result in weight increased).

Psychiatric Disorders

Not known: Affective disorder (including depressed mood, euphoric mood, affect lability, drug dependence, suicidal ideation), psychotic disorder (including mania, delusion, hallucination and schizophrenia), mental disorder, personality change, confusional state, anxiety, mood swings, abnormal behaviour, insomnia, irritability.

Nervous System Disorders

Not known: Epidural lipomatosis, intracranial pressure increased (with papilloedema [benign intracranial hypertension]), seizure, amnesia, cognitive disorder, dizziness, headache.

Eye Disorders

Uncommon: Vision blurred (see also **section 4.4**).

Not known: Chorioretinopathy, cataract, glaucoma, exophthalmos.

Ear and Labyrinth Disorders

Not known: Vertigo.

Cardiac Disorders

Not known: Cardiac failure congestive (in susceptible patients), arrhythmia.

Vascular Disorders

Not known: Thrombosis, hypertension, hypotension.

Respiratory, Thoracic and Mediastinal Disorders

Not known: Pulmonary embolism, hiccups.

Gastrointestinal Disorders

Not known: Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage), intestinal perforation, gastric haemorrhage, pancreatitis, oesophagitis ulcerative, oesophagitis, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea.

Hepatobiliary Disorders

Not known: Hepatitis^d.

Skin and Subcutaneous Tissue Disorders

Not known: Angioedema, hirsutism, petechiae, ecchymosis, skin atrophy, erythema, hyperhidrosis, skin striae, rash, pruritus, urticaria, acne, skin hypopigmentation.

Musculoskeletal and Connective Tissue Disorders

Not known: Muscular weakness, myalgia, myopathy, muscle atrophy, osteoporosis, osteonecrosis, pathological fracture, neuropathic arthropathy, arthralgia, growth retardation.

Reproductive System and Breast Disorders

Not known: Menstruation irregular.

General Disorders and Administration Site Conditions

Not known: Impaired healing, oedema peripheral, fatigue, malaise, injection site reaction.

Investigations

Not known: Intraocular pressure increased, carbohydrate tolerance decreased, blood potassium decreased, urine calcium increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, suppression of reactions to skin tests^f.

Injury, Poisoning and Procedural Complications

Not known: Spinal compression fracture, tendon rupture.

^a Including increased susceptibility to and severity of infections, masking of infections and latent infections (e.g., tuberculosis) becoming active.

^b Particularly in times of stress, as in trauma, surgery or illness.

- ^c Manifestations of latent diabetes mellitus.
- ^d Hepatitis has been reported with IV administration (see **section 4.4**).
- ^e Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see **section 4.4**).
- ^f Not a MedDRA preferred term.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Reports of acute toxicity and metabolic disturbances with glucocorticoids are rare but do occur. There is no clinical syndrome of acute overdosage with SOLU-MEDROL Powder for Injection. Acute overdose may possibly aggravate pre-existing disease states such as ulceration of the gastrointestinal tract, electrolyte disturbances, infections, diabetes and oedema. Repeated high doses of methylprednisolone have caused hepatic necrosis and an increase in amylase. Bradyarrhythmias, ventricular arrhythmias and cardiac arrest have been observed in cases of intravenous administration of high doses of methylprednisolone.

Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state. The possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time.

In the event of an overdose, no specific antidote is available; treatment is symptomatic and supportive, including respiratory and cardiovascular function. In chronic toxicity, fluids and electrolytes should be monitored closely. Serum levels are not clinically useful. Methylprednisolone is dialysable.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

5.2 Pharmacokinetic properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Absorption

After an intravenous infusion of SOLU-MEDROL, 30 mg/kg over a 20-minute period or 1 g over 30 to 60 minutes, peak methylprednisolone plasma concentrations of approximately 20 mcg/mL were achieved. Peak methylprednisolone levels of 42-47 mcg/100 mL were reported following a single 40mg IV bolus injection to six adult male volunteers.

Peak methylprednisolone plasma levels of 33.67 mcg/100 mL were achieved in two hours after a single 40 mg IM injection to 22 adult male volunteers.

Although with intramuscular (IM) injection lower peak levels are obtained than with intravenous (IV) injection, the plasma levels persist longer such that the extent of methylprednisolone absorption is equivalent with either route of administration.

Distribution

Methylprednisolone is widely distributed throughout the body and is described by a two-compartment model. Its apparent volume of distribution is approximately 1.4 mL/kg and its total clearance is approximately 5 to 6 mL/min/kg.

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

SOLU-MEDROL readily crosses the blood-brain barrier into the central nervous system with peak CSF levels being 5-6% of the corresponding plasma levels. Methylprednisolone peak CSF levels occurred within five minutes to one hour after IV administration of a 500 mg dose to patients with lupus cerebritis.

Methylprednisolone and the sodium succinate salt crosses the placental barrier. Although there is no data regarding methylprednisolone passage into breast milk of humans, it is present in breast milk of animals.

Biotransformation

SOLU-MEDROL, the sodium succinate ester of methylprednisolone, is rapidly and extensively hydrolysed *in vivo* by cholinesterases to free methylprednisolone.

In humans, methylprednisolone is metabolised in the liver to inactive metabolites, the major ones being 20 β -hydroxymethylprednisolone and 20 α -hydroxy-6 α -methylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. For a list of drug interactions based on CYP3A4-mediated metabolism (see **section 4.5**).

Elimination

The mean elimination half-life ranges for total methylprednisolone is in the range of 1.8 to 5.2 hours.

The plasma protein binding of methylprednisolone in humans is approximately 77%.

Total body clearance following intravenous or intramuscular injection of methylprednisolone to healthy adult volunteers is approximately 15-16 L/hr. In adult volunteers receiving 40 mg SOLU-MEDROL, either IM or IV, renal clearance is 0.61-0.83 L/hr. Methylprednisolone clearance is altered by concurrent administration of troleandomycin, erythromycin, rifampin, anti-convulsants, and theophylline.

Following IV administration of radiolabelled 6 α -methylprednisolone to six cancer patients, 75% of total reactivity was recovered in the urine after 96 hours and 9% in the faeces after five days. Twenty percent of the total dose was excreted in the bile, but the time course was not cited.

5.3 Preclinical safety data

Genotoxicity

Methylprednisolone has not been formally evaluated for genotoxicity. However, methylprednisolone sulfonate, which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* at 250 to 2,000 $\mu\text{g}/\text{plate}$, or in a mammalian cell gene mutation assay using Chinese hamster ovary cells at 2,000 to 10,000 $\mu\text{g}/\text{mL}$. Methylprednisolone suleptanate did not induce unscheduled DNA synthesis in primary rat hepatocytes at 5 to 1,000 $\mu\text{g}/\text{mL}$. Moreover, a review of published data indicates that prednisolone farnesylate (PNF), which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* and *Escherichia coli* strains at 312 to 5,000 $\mu\text{g}/\text{plate}$. In a Chinese hamster fibroblast cell line, PNF produced a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested 1,500 $\mu\text{g}/\text{mL}$.

Carcinogenicity

Methylprednisolone has not been formally evaluated in rodent carcinogenicity studies. Variable results have been obtained with other glucocorticoids tested for carcinogenicity in mice and rats. However, published data indicate that several related glucocorticoids including budesonide, prednisolone, and triamcinolone acetonide can increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water to male rats. These tumorigenic effects occurred at doses which were less than the typical clinical doses on a mg/m^2 basis.

Reproductive Toxicity

In animal studies for embryotoxic effects of methylprednisolone, no teratogenic effect was observed in mice or rats at daily intraperitoneal doses of 125 $\text{mg}/\text{kg}/\text{day}$ or 100 $\text{mg}/\text{kg}/\text{day}$, respectively. In rats, methylprednisolone was teratogenic when administered subcutaneously at a dose of 20 $\text{mg}/\text{kg}/\text{day}$. Methylprednisolone aceponate was teratogenic when given subcutaneously to rats at a dose of 1.0 $\text{mg}/\text{kg}/\text{day}$. Male rats were administered corticosterone at doses of 0, 10, and 25 $\text{mg}/\text{kg}/\text{day}$ by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 $\text{mg}/\text{kg}/\text{day}$ after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids such as

methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), and intra-uterine growth retardation.

Preclinical Repeated-Dose Toxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SOLU-MEDROL ACT-O-VIAL 40 mg/mL powder for injection

Powder for injection compartment:

- monobasic sodium phosphate
- dibasic sodium phosphate
- lactose monohydrate
- sodium hydroxide.

Diluent compartment:

- water for injections.

SOLU-MEDROL ACT-O-VIAL 125 mg/2 mL powder for injection

Powder for injection compartment:

- monobasic sodium phosphate
- dibasic sodium phosphate
- sodium hydroxide.

Diluent compartment:

- water for injections.

SOLU-MEDROL ACT-O-VIAL 500 mg/4 mL

Powder for injection compartment:

- monobasic sodium phosphate
- dibasic sodium phosphate
- sodium hydroxide.

Diluent compartment:

- water for injections

SOLU-MEDROL 1 g powder for injection

Powder for injection vial:

- sodium phosphate monobasic monohydrate
- dibasic sodium phosphate
- sodium hydroxide.

Diluent vial:

- water for injections
- benzyl alcohol as preservative 140.4 mg.

SOLU-MEDROL 2 g powder for injection

Powder for injection vial:

- monobasic sodium phosphate monohydrate
- sodium phosphate dibasic
- sodium hydroxide.

Diluent vial:

- water for injections
- benzyl alcohol as preservative 280.8 mg.

6.2 Incompatibilities

The IV compatibility and stability of methylprednisolone sodium succinate solutions and with other drugs in intravenous admixtures is dependent on admixture pH, concentration, time, temperature and the ability of methylprednisolone to solubilise itself. Thus, to avoid compatibility and stability problems, whenever possible, it is recommended that SOLU-MEDROL (methylprednisolone sodium succinate) be administered separate from other drugs and as either IV medication chamber, or as an IV “piggy-back” solution.

Drugs that are physically incompatible in solution with methylprednisolone sodium succinate include, but are not limited to: allopurinol sodium, doxapram hydrochloride, tigecycline, diltiazem hydrochloride, calcium gluconate, vecuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol.

6.3 Shelf life

SOLU-MEDROL ACT-O-VIAL 40 mg/mL powder for injection: 24 months.

SOLU-MEDROL ACT-O-VIAL 125 mg/2 mL powder for injection: 36 months.

SOLU-MEDROL ACT-O-VIAL 500 mg/4 mL injection with diluent: 36 months.

SOLU-MEDROL 1 g powder for injection: 60 months.

SOLU-MEDROL 2 g powder for injection: 60 months.

6.4 Special precautions for storage

Store unconstituted product below 25°C. Protect from light.

When reconstituted use only the accompanying diluent. The diluent provided with the ACT-O-VIAL system is sterile Water for Injections. The diluent provided with the 1 g and 2 g vials is bacteriostatic Water for Injections with benzyl alcohol. The resulting solution should be used immediately. Discard any unused portion.

6.5 Nature and contents of container

SOLU-MEDROL is available in the following pack sizes:

- SOLU-MEDROL ACT-O-VIAL 40 mg/mL powder for injection: two-compartment vial in pack sizes of 1 or 20 dose units
- SOLU-MEDROL ACT-O-VIAL 125 mg/2 mL powder for injection: two-compartment vial in pack sizes of 1 or 25 dose units
- SOLU-MEDROL ACT-O-VIAL 500 mg/4 mL injection with diluent: two-compartment glass ampoule in a pack size of 1
- SOLU-MEDROL 1 g powder for injection: 1 glass vial
- SOLU-MEDROL 2 g powder for injection: 1 glass vial.

Not all presentations may be marketed.

SOLU-MEDROL is available in preservative and preservative-free formulations.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Ltd
P O Box 3998
Auckland
NEW ZEALAND
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

SOLU-MEDROL ACT-O-VIAL 40 mg/mL powder for injection: 26 July 1973
SOLU-MEDROL ACT-O-VIAL 125 mg/2 mL powder for injection: 21 January 1972
SOLU-MEDROL ACT-O-VIAL 500 mg/4 mL injection with diluent: 16 September 1999
SOLU-MEDROL 1 g powder for injection: 21 January 1972
SOLU-MEDROL 2 g powder for injection: 21 January 1972

10. DATE OF REVISION OF THE TEXT

10 December 2020

Summary Table of Changes

Section changed	Summary of new information
4.2	Removal of the indication for seasonal or perennial allergic rhinitis.

® SOLU-MEDROL is a registered trademark