SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SOLU-MEDROL™ 40 mg Injection

SOLU-MEDROL™ 125 mg Injection

SOLU-MEDROL™ 500 mg Injection

SOLU-MEDROL™ 1 000 mg Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SOLU-MEDROL 40 mg: Each 1 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone.

SOLU-MEDROL 125 mg: Each 2 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone.

SOLU-MEDROL 500 mg: Each 8 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone.

SOLU-MEDROL 1 000 mg: Each 16 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 1 000 mg methylprednisolone.

SOLU-MEDROL 40 mg: Contains sugar (sucrose).

SOLU-MEDROL 125 mg: Sugar free.

SOLU-MEDROL 500 mg: Sugar free.

SOLU-MEDROL 1 000 mg: Sugar free.

Excipients with known effect

Each 1 mL SOLU-MEDROL 40 mg injection contain 23,7 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white freeze-dried cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SOLU-MEDROL is indicated for use in the following when the oral route is not suitable:

1. Endocrine disorders

Primary and secondary adrenocortical insufficiency. (Hydrocortisone or cortisone is the medicine of choice; synthetic analogues must be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

2. Corticosteroid responsive diseases including

2.1. Rheumatic disorders

Acute rheumatic carditis.

2.2. Collagen disease (immune complex disease)

During exacerbation in selected cases of:

Systemic lupus erythematosus and lupus nephritis.

Systemic dermatomyositis (polymyositis).

Polyarteritis nodosa.

2.3. Dermatological disorders

In steroid-responsive cases of severe dermatological disorders.

2.4. Allergic states

Control of severe or incapacitating allergic states necessitating intravenous therapy.

2.5. Gastrointestinal diseases

Control of severe or incapacitating ulcerative colitis necessitating intravenous therapy.

2.6. Haematological disorders

Secondary thrombocytopenia of immunological origin in adults in whom IV therapy is indicated.

Idiopathic thrombocytopenic purpura in adults (IV administration only; IM administration is contraindicated).

2.7. Nervous system

Cerebral oedema due to tumour, either primary or metastatic and/or associated with surgical procedures, radiation therapy or head trauma.

Acute exacerbations of multiple sclerosis.

2.8. Acute spinal cord injury

As adjunctive therapy in the treatment of the symptoms of acute spinal cord injury. The treatment should begin within eight hours of injury.

2.9. Cardiovascular conditions

Shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present. (Hydrocortisone is generally the medicine of choice.)

2.10. Organ transplantation

To prevent or treat rejection of organ transplantation.

2.11. Neoplastic diseases

For the palliative management of leukaemias and lymphomas in adults.

As adjunctive therapy for nausea and vomiting associated with cancer therapy.

4.2 Posology and method of administration

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.

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

Posology

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

For corticosteroid responsive diseases in exacerbation, and unresponsive to standard therapy, pulse dosing may be used.

Suggested dosing schedules are:

Systemic lupus erythematosus: 1 g/day for 3 days IV

Multiple sclerosis: 1 g/day for 3 days IV or 1 g/day for 5 days IV

Oedematous states (e.g. lupus nephritis): 30 mg/kg every other day for 4 days IV or 1 g/day for 3,5 or 7 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 the patient's condition dictates.

Acute spinal cord injury

As adjunctive therapy in the treatment of acute spinal cord injury, administer intravenously, 30 mg methylprednisolone per kilogram of body weight in a bolus dose over a 15 minute period, followed by a 45 minute pause, and then a continuous infusion of 5,4 mg/kg per hour for 23 hours and then stopped abruptly. There should be a separate intravenous site for the infusion pump. The treatment should begin within eight hours of injury.

As adjunctive therapy for the prevention of nausea and vomiting associated with cancer chemotherapy the suggested dosage schedules are:

Mild to moderate emetogenic chemotherapy

Administer 250 mg of SOLU-MEDROL IV over at least 5 minutes, one hour before chemotherapy, at the

initiation of chemotherapy, and at the time of discharge.

Severely emetogenic chemotherapy

Administer 250 mg of SOLU-MEDROL IV over at least 5 minutes with appropriate doses of metoclopramide or a butyrophenone one hour before chemotherapy, then 250 mg SOLU-MEDROL IV at the initiation of chemotherapy and at time of discharge.

In other indications, the initial dose will vary from 10 to 500 mg IV depending on the severity of the disorder 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 5 minutes, and if greater than 250 mg, should be given over at least 30 minutes. Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical condition.

Dosage must be decreased or discontinued gradually when SOLU-MEDROL has been administered for more than a few days.

Routine laboratory studies must be performed such as urinalysis, 2-hour postprandial blood sugar, determination of blood pressure and body mass, and a chest X-ray should be taken at regular intervals during prolonged therapy. Upper gastrointestinal endoscopy may be indicated in patients with an ulcer history or significant dyspepsia.

Paediatric population

Dosage must be reduced for infants and children but should be governed by the severity of the condition and response of the patient rather than by the age or size. It should, however, not be less than 0,5 mg per kg every 24 hours.

Method of administration

For intravenous injection or infusion or intramuscular injection.

To avoid compatibility and stability problems, it is recommended that SOLU-MEDROL be administered

separately from other medicines and as either an IV push, through an IV medicine chamber, or as an IV "piggy-back" solution (see section 6.6 for preparation and use).

4.3 Contraindications

SOLU-MEDROL is contraindicated:

- in patients with known hypersensitivity to methylprednisolone or any of the excipients of SOLU-MEDROL listed in section 6.1
- in patients with systemic fungal infections
- for use by the intrathecal route of administration
- for epidural route of administration
- Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids
- Unless considered lifesaving SOLU-MEDROL should not be given to patients with acute psychosis, peptic ulcer, or osteoporosis
- Traumatic brain injury

4.4 Special warnings and precautions for use

Severe adverse effects have been reported in association with the intrathecal/epidural routes of administration including arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, convulsions, sensory disturbances. The frequency of these adverse reactions is not known.

Immunosuppressant effects/increased susceptibility to infections

Corticosteroids such as SOLU-MEDROL may increase susceptibility to infection, may mask signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids such as SOLU-MEDROL 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 such as SOLU-MEDROL alone or in combination with other immunosuppressive medicines that affect cellular immunity, humoral immunity, or neutrophil function. These infections can be severe and may be fatal. With increasing doses of SOLU-MEDROL, the rate of occurrence of infectious

complications increases.

Persons who are on medicines which suppress the immune system such as SOLU-MEDROL are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids including SOLU-MEDROL.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving SOLU-MEDROL. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of SOLU-MEDROL; however, the response to such vaccines may be diminished.

The use of SOLU-MEDROL in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which SOLU-MEDROL is used in conjunction with appropriate anti-tuberculosis regimen.

The use of SOLU-MEDROL in patients with latent tuberculosis may activate the tuberculosis. In patients with tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged SOLU-MEDROL therapy, these patients should receive chemoprophylaxis.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy such as SOLU-MEDROL. Discontinuation of SOLU-MEDROL may result in clinical remission.

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended and a systematic review concluded that short-course, high-dose corticosteroids did not support use. However, meta-analyses, and a review suggest that longer courses (5 – 11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor-dependent septic shock.

Increased mortality may occur in some subgroups at higher risk i.e. elevated creatinine greater than 2,0 mg % (170 µmol/L) or secondary infections.

Immune system effects

Hypersensitivity reactions (e.g. angioedema) may occur, including skin reactions and anaphylactic/anaphylactoid reactions. Appropriate precautionary measures should be taken prior to administration of SOLU-MEDROL, especially when the patient has a history of allergy to any medicine.

Endocrine effects

In patients on SOLU-MEDROL therapy of 2 to 3 weeks or more who are subjected to stress, increased dosage of corticosteroids before, during and after the stressful situation may be indicated.

Corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency).

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

SOLU-MEDROL-induced secondary adrenocortical insufficiency may be minimised by gradual reduction of dosage. This type of insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, SOLU-MEDROL therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

A steroid “withdrawal syndrome” may also occur following abrupt discontinuance of glucocorticoids and may cause anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension.

Because glucocorticoids such as SOLU-MEDROL can produce or aggravate Cushing’s syndrome, SOLU-MEDROL should be avoided in patients with Cushing’s disease.

There is an enhanced effect of corticosteroids including SOLU-MEDROL on patients with hypothyroidism.

Metabolism and nutrition

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

Psychiatric effects

Psychic derangements may appear when corticosteroids including SOLU-MEDROL 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 such as SOLU-MEDROL.

Potentially severe psychiatric adverse reactions may occur with corticosteroids such as SOLU-MEDROL (see section 4.8, Psychiatric disorders). 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 including SOLU-MEDROL; 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 SOLU-MEDROL.

Nervous system effects

SOLU-MEDROL should be used with caution in patients with seizure disorders.

SOLU-MEDROL should be used with caution in patients with myasthenia gravis (see myopathy statement in Musculoskeletal effects section).

Although controlled clinical trials have shown corticosteroids including SOLU-MEDROL to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids including SOLU-MEDROL 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. The onset of symptoms is usually gradual. The symptoms may include back pain and sensory or motor disorders.

Ocular effects

SOLU-MEDROL should not be used in patients with ocular herpes simplex because of possible corneal perforation.

Prolonged use of corticosteroids including SOLU-MEDROL 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 such as SOLU-MEDROL.

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

Patients on repeated/prolonged courses of steroids should have regular ophthalmic examination/assessments.

Cardiac effects

Adverse effects of glucocorticoids including SOLU-MEDROL on the cardiovascular system, such as dyslipidaemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects especially if high doses and prolonged courses are used. Accordingly, SOLU-MEDROL 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 dysrhythmias, and/or circulatory collapse, and/or cardiac arrest following the rapid administration of large intravenous doses of SOLU-MEDROL (more than 0,5 g administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of SOLU-MEDROL and may be unrelated to the speed or duration of infusion.

Systemic SOLU-MEDROL 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 including SOLU-MEDROL. As a result, SOLU-MEDROL should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

SOLU-MEDROL should be used with caution in patients with hypertension as SOLU-MEDROL may further increase the blood pressure.

Gastrointestinal effects

There is no universal agreement on whether corticosteroids such as SOLU-MEDROL 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. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

SOLU-MEDROL should be used with caution in patients with ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection, diverticulitis, intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary effects

High doses of SOLU-MEDROL may produce acute pancreatitis.

Musculoskeletal effects

An acute myopathy has been reported with the use of high doses of corticosteroids including SOLU-MEDROL, 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 medicines (e.g. pancuronium). This acute myopathy is generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping SOLU-MEDROL may require weeks to years.

Osteoporosis is a common but insufficiently recognised adverse effect associated with a long-term use of glucocorticoid including SOLU-MEDROL.

Renal and urinary disorders

SOLU-MEDROL should be used with caution in patients with renal insufficiency.

Investigations

Corticosteroids such as SOLU-MEDROL can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. Corticosteroids including SOLU-MEDROL increase calcium excretion.

Injury, poisoning and procedural complications

SOLU-MEDROL is contraindicated in treatment of traumatic brain injury; a multicentre study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered SOLU-MEDROL compared to placebo (see section 4.3).

Other

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Aspirin and nonsteroidal anti-inflammatory drugs should be used cautiously in conjunction with SOLU-

MEDROL.

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

Excipients with known effect

SOLU-MEDROL 40 mg injection contains sucrose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not be given SOLU-MEDROL.

Paediatric population

The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in paediatric patients. Although normal therapeutic doses of this medicine ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic 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 SOLU-MEDROL therapy should be carefully observed.

Growth may be suppressed in children receiving long-term SOLU-MEDROL therapy. Alternate-day SOLU-MEDROL therapy may avoid or minimise this side effect.

Infants and children on prolonged SOLU-MEDROL therapy are at special risk from raised intracranial pressure.

High doses of SOLU-MEDROL may produce pancreatitis in children.

4.5 Interaction with other medicines and other forms of interaction

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

CYP3A4 inhibitors

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

CYP3A4 inducers

Medicines that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medicines that are substrates for CYP3A4. Co-administration may require an increase in SOLU-MEDROL dosage to achieve the desired result.

CYP3A4 substrates

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

Non-CYP3A4-mediated effects

Other interactions and effects that occur with SOLU-MEDROL are described in Table 1 below.

Table 1 provides a list and descriptions of the most common and/or clinically important medicine interactions or effects with *SOLU-MEDROL.*

Table 1. Important medicine or substance interactions/effects with SOLU-MEDROL

Medicine class or type	**Interaction/effect**

MEDICINE or SUBSTANCE	
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of SOLU-MEDROL to increase the acetylation rate and clearance of isoniazid (see CYP3A4 inhibitors above for the results of the interaction).
Antibiotic, antitubercular - RIFAMPICIN	CYP3A4 INDUCER (see CYP3A4 inducers above for the results of the interaction).
Anticoagulants (oral) - WARFARIN	The effect of SOLU-MEDROL on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE) (see CYP3A4 inducers and CYP3A4 substrates above for the results of the interaction).
Anticonvulsants - PHENOBARBITAL (PHENOBARBITONE) - PHENYTOIN	CYP3A4 INDUCERS (see CYP3A4 inducers above for the results of the interaction).
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking medicines (see

	section 4.4, Musculoskeletal effects). 2) Antagonism of the neuromuscular blocking effects of all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic medicines may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction). 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations. Steroids are also known inducers of CYP

	enzymes in animal models and *in vitro* studies. Dexamethasone, at doses similar to those used in clinical practice, has been shown to increase CYP3A4 activity in both healthy volunteers and human hepatocyte cultures. Therefore, corticosteroids may induce the metabolism of HIV-protease inhibitors by upregulation of CYP3A4.
Aromatase inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium channel blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR (see CYP3A4 inhibitors above for the results of the interaction).
Immunosuppressant - CICLOSPORIN	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction). 1) Mutual inhibition of metabolism occurs

	with concurrent use of ciclosporin and SOLU-MEDROL, which may increase the plasma concentrations of either or both medicines. Therefore, it is possible that adverse events associated with the use of either medicine alone may be more likely to occur upon co-administration. 2) Convulsions have been reported with concurrent use of SOLU-MEDROL and ciclosporin.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES (see CYP3A4 substrates above for the results of the interaction).
Macrolide antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Macrolide antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR (see CYP3A4 inhibitors above for the results of the interaction).
NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) SOLU-MEDROL may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of SOLU-MEDROL treatment can lead to raised salicylate

	serum levels, which could lead to an increased risk of salicylate toxicity.
Potassium-depleting medicines	When corticosteroids are administered concomitantly with potassium-depleting medicines (i.e. diuretics), 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been demonstrated. Adequate human reproductive studies have not been performed with methylprednisolone.

Animal studies have shown that corticosteroids such as SOLU-MEDROL, may cause foetal malformations. There is no evidence that corticosteroids cause an increased incidence of congenital anomalies when given to pregnant women, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation.

SOLU-MEDROL is teratogenic in animals.

Some corticosteroids readily cross the placenta and cause low birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be diminished by administering lower SOLU-MEDROL 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. Hypoadrenalism may occur in neonates following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important.

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

Cataracts have been observed in infants born to mothers treated with corticosteroids including SOLU-MEDROL during pregnancy.

Benzyl alcohol can cross the placenta (see section 4.4).

Breastfeeding

Safety of SOLU-MEDROL in lactation has not been demonstrated. Corticosteroids such as SOLU-MEDROL are excreted in breast milk. Corticosteroids such as SOLU-MEDROL distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants.

Fertility

Corticosteroids including SOLU-MEDROL have been shown to impair fertility in animal studies.

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 may occur during treatment with SOLU-MEDROL. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse reactions are listed by system organ class and ranked by frequency where possible.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Not known	Opportunistic infection, infection

Blood and lymphatic system disorders	Not known	Leucocytosis
Immune system disorders	Not known	Medicine hypersensitivity (including anaphylactic reaction and anaphylactoid reaction)
Endocrine disorders	Not known	Cushingoid, hypopituitarism, steroid withdrawal syndrome
Metabolism and nutrition disorders	Not known	Lipomatosis, sodium retention, fluid retention, hypokalaemic alkalosis, dyslipidaemia, impaired glucose tolerance, diabetes mellitus, increased insulin requirement (or oral hypoglycaemic medicines in diabetics), negative nitrogen balance (due to protein catabolism), increased blood urea, increased appetite (which may result in increased weight)
Psychiatric disorders	Not known	Affective disorder (including depressed mood, euphoric mood, affect lability, medicine 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 with neurological deficits/ paraesthesia/paralysis, increased intracranial pressure (with papilloedema [benign intracranial hypertension]), convulsion, amnesia, cognitive disorder, dizziness, headache
Eye disorders	Not known	Central serous chorioretinopathy with retinal detachment, cataract, glaucoma, exophthalmos
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Less frequent	Dysrhythmia, bradycardia
	Not known	Congestive cardiac failure (in susceptible patients)
Vascular disorders	Not known	Venous 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, peritonitis, ulcerative oesophagitis, oesophagitis, abdominal distention, abdominal pain, diarrhoea, dyspepsia, nausea

Skin and subcutaneous tissue disorders	Not known	Angioedema, peripheral oedema, 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, bone fracture, neuropathic arthropathy, arthralgia, growth retardation
Reproductive system and breast disorders	Not known	Irregular menstruation, amenorrhoea
General disorders and administration site conditions	Not known	Impaired healing, fatigue, malaise, injection site reaction
Investigations	Not known	Increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood alkaline phosphatase (ALP), increased urine calcium, decreased blood potassium, decreased carbohydrate tolerance, increased intraocular pressure, suppression of reactions to skin tests*
Injury, poisoning and procedural complications	Not known	Spinal compression fracture, tendon rupture
* Not a MedDRA PT		

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids.

In the event of overdosage, no specific antidote is available; treatment should be symptomatic and supportive. Methylprednisolone is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.5.1 Corticosteroids and analogues

Methylprednisolone has anti-inflammatory steroid activity.

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two medicines are equivalent in biologic activity. The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate as indicated by the 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 a 40 mg intramuscular dose of methylprednisolone sodium succinate to fourteen healthy adult male volunteers, the average peak concentration of 454 ng/mL was achieved at 1 hour. At 12 hours, the methylprednisolone plasma concentration has declined to 31,9 ng/mL. No methylprednisolone was detected 18 hours after dosing. Based on area-under-the-time-concentration curve, an indication of total medicine absorbed, intramuscular methylprednisolone sodium succinate was found to be equivalent to the same dose administered intravenously.

Results of a study demonstrated that the sodium succinate ester of methylprednisolone is rapidly and extensively converted to the active methylprednisolone moiety after all routes of administration. Extent of absorption of free methylprednisolone following IV and IM administrations were found to be equivalent and significantly greater than those following administration of the oral solution and oral methylprednisolone tablets. Since the extent of methylprednisolone absorbed following the IV and IM treatment was equivalent in spite of the greater amount of the hemisuccinate ester reaching the general circulation after IV administration, it appears that the ester is converted in the tissue after IM injection with subsequent absorption as free methylprednisolone.

Distribution

Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, is secreted in breast milk and crosses the placenta. 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 metabolised in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4 (see section 4.5).

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

Elimination

The mean elimination half-life for total methylprednisolone is in the range of 1,8 to 5,2 hours. Total clearance is approximately 5 to 6 mL/min/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SOLU-MEDROL 40 mg and 125 mg

Sucrose (40 mg only)

Monobasic sodium phosphate monohydrate

Dibasic sodium phosphate dried

Water for injection

SOLU-MEDROL 500 mg and 1000 mg

Monobasic sodium phosphate monohydrate

Dibasic sodium phosphate dried

0,9 % m/v Benzyl alcohol (preservative)

Water for injection

6.2 Incompatibilities

To avoid compatibility and stability problems, it is recommended that SOLU-MEDROL be administered separately from other medicines that are administered via the IV route of administration. Medicines that are physically incompatible in solution with SOLU-MEDROL 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 40 mg: 24 months.

SOLU-MEDROL 125 mg: 24 months.

SOLU-MEDROL 500 mg: 60 months.

SOLU-MEDROL 1 000 mg: 60 months.

6.4 Special precautions for storage

Unreconstituted medicine:

Store at or below 25 °C.

Reconstituted solution:

SOLU-MEDROL 40 mg

Store reconstituted solution below 25 °C and use immediately or store reconstituted solution at 2 to 8°C and use within 48 hours.

SOLU-MEDROL 125 mg

Store reconstituted solution below 25 °C and use within 24 hours or store reconstituted solution at 2 to 8°C and use within 72 hours.

SOLU-MEDROL 500 mg and 1000 mg

Store reconstituted solution below 25 °C and use within 12 hours.

6.5 Nature and contents of container

SOLU-MEDROL is available in the following strengths:

40 mg Act-O-Vial

125 mg Act-O-Vial

500 mg Vial with Bacteriostatic Water for Injection

1 000 mg Vial with Bacteriostatic Water for Injection

6.6 Special precautions for disposal and other handling

Preparation of solutions

To prepare solutions for intravenous infusion, first reconstitute SOLU-MEDROL as directed. Therapy may be initiated by administering SOLU-MEDROL intravenously over a period of at least 5 minutes (for doses up to 250 mg) to at least 30 minutes (for doses of 250 mg or more). Subsequent doses may be withdrawn and administered similarly.

If desired, SOLU-MEDROL may be administered in dilute solutions by admixing the reconstituted medicine with Dextrose 5 % in Water, Normal Saline, Dextrose 5 % in 0,45 % or 0,9 % m/v Sodium Chloride. Chemical and physical in-use stability of the reconstituted and further diluted solution has been demonstrated for 24 hours at 2 to 8°C. It should be used within 3 hours if stored at 20 to 25°C.

Directions for using the Act-O-Vial

1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering centre of stopper.
4. Sterilise top of stopper with a suitable germicide.
5. Insert needle through centre of plunger-stopper until tip is just visible.
6. Invert vial and withdraw dose.

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

SOLU-MEDROL 40 mg: D/21.5.1/135

SOLU-MEDROL 125 mg: D/21.5.1/136

SOLU-MEDROL 500 mg: L/21.5.1/25

SOLU-MEDROL 1 000 mg: L/21.5.1/26

Bacteriostatic Water for Injection: H/34/60

9. DATE OF FIRST AUTHORISATION

SOLU-MEDROL 40 mg: 17 December 1971

SOLU-MEDROL 125 mg: 17 December 1971

SOLU-MEDROL 500 mg: 22 February 1978

SOLU-MEDROL 1 000 mg: 22 February 1978

Bacteriostatic Water for Injection: 20 October 1975

10. DATE OF REVISION OF THE TEXT

27 March 2025

Manufacturer: Pfizer Manufacturing Belgium NV, Puurs-Sint-Amands, Belgium

BOTSWANA: S2

SOLU-MEDROL 40 mg: Reg. No.: B9312160

SOLU-MEDROL 125 mg: Reg. No.: B9312165

SOLU-MEDROL 500 mg: Reg. No.: B9312170

SOLU-MEDROL 1 000 mg: Reg. No.: B9312175

NAMIBIA: NS2

SOLU-MEDROL 40 mg: Reg. No.: 90/21.5.1/001362

SOLU-MEDROL 125 mg: Reg. No.: 90/21.5.1/001360

SOLU-MEDROL 500 mg: Reg. No.: 90/21.5.1/001363

SOLU-MEDROL 1 000 mg: Reg. No.: 90/21.5.1/001359