Solu-Medrol®

Methylprednisolone Sodium Succinate

PAA143934
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- Acute gouty arthritis
- Psoriatic arthritis
- Ankylosing spondylitis

- *Collagen diseases (immune 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
- Goodpasture's syndrome

- *Dermatologic diseases*
- Pemphigus
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Exfoliative dermatitis
- Bullous dermatitis herpetiformis
- Severe seborrheic dermatitis
- Severe psoriasis
- Mycosis fungoides
- Urticaria

- *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
- Seasonal or perennial allergic rhinitis
- Drug hypersensitivity reactions
- Urticarial transfusion reactions
- Acute noninfectious laryngeal edema (epinephrine 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

- *Gastrointestinal diseases*
To tide the patient over a critical period of the disease in:
- Ulcerative colitis (systemic therapy)
- Regional enteritis (systemic therapy)

- *Respiratory diseases*
- Pulmonary sarcoidosis
- Beryllosis
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
- Loeffler's syndrome not manageable by other means
- Aspiration pneumonitis

- *Edematous states*
To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Immunosuppressive treatment

- *Organ transplantation*

Treatment of hematological and oncological disorders

- *Hematologic disorders*
- Acquired (autoimmune) hemolytic anemia
- Idiopathic thrombocytopenia purpura in adults (intravenous only; intramuscular administration is contraindicated)
- Secondary thrombocytopenia in adults
- Erythroblastopenia (RBC anemia)
- Congenital (erythroid) hypoplastic anemia

- *Oncological diseases*
For palliative management of:
- Leukemias and lymphomas in adults
- Acute leukemia of childhood

Others

- Nervous system
- Cerebral edema from tumor – 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.
- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
- Trichinosis with neurological or myocardial involvement
- Prevention of nausea and vomiting associated with cancer chemotherapy

Endocrine disorders

- Primary or secondary adrenocortical insufficiency
- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis
- Hypercalcaemia associated with cancer

4.2 Posology and method of administration

Posology
See table below for recommended dosages.

Recommended dosages of methylprednisolone sodium succinate

Indication	Posology
As adjunctive therapy in life-threatening conditions	The recommended dose is 30 mg per kg., given intravenously over a period of at least 30 minutes. This dose may be repeated in the hospital every 4 to 6 hours for 48 hours depending on the clinical necessity (see section 4.4).
"PULSE-THERAPY" in case of very serious exacerbation and/or unresponsive to standard therapy, as nonsteroidal inflammatory means, gold salts and penicillamine.	Suggested schedules: Rheumatoid arthritis: - 1 g/day intravenous for 1, 2, 3 or 4 days or - 1 g./month intravenous for 6 months. As high doses of corticosteroids can cause an arythmogenic action, this therapy should be restricted to hospitals, which dispose of an electrocardiograph and a defibrillator. The regimen should be administered over at least 30 minutes and may be repeated if no improvement has been reported within one week after therapy or if the patient's condition dictates.
Prevention of nausea and vomiting associated with cancer chemotherapy	Suggested schedules: - Mild to moderately emetogenic chemotherapy: Administer 250 mg intravenous over at least 5 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 for increased effect. - Severely emetogenic chemotherapy: Administer 250 mg intravenous over at least 5 minutes with appropriate doses of metoclopramide or a butyrophenone one hour before chemotherapy, before 250 mg intravenous at the initiation of therapy and at time of discharge.

Indication	Posology
Acute spinal cord injury	**The treatment should begin within eight hours of injury.** For patients initiated on treatment within 3 hours of injury: Start with an I.V. bolus dose of 30 mg methylprednisolone per kilogram of body weight over a 15 minute period under continuous medical supervision. After the bolus injection comes a 45 minute pause, followed by a continuous infusion of 5,4 mg/kg per hour for 23 hours. For patients initiated on treatment within 3 to 8 hours of injury: Start with an I.V. bolus dose of 30 mg methylprednisolone per kilogram of body weight once a 15 minute period under continuous medical supervision. After the bolus injection comes a 45 minute pause, followed by a continuous infusion of 5,4 mg/kg per hour for 47 hours. For the infusion pump, one should preferably choose another intravenous site than for the bolus injection. The administration rate of the bolus injection may only be used for this indication, under ECG-monitoring and with an available defibrillator. The administration of a high dose of methylprednisolone in bolus intravenously (doses of more than 500 mg over a period of less than 10 minutes) may cause arrhythmias, circulatory collapse and cardiac arrest.
In other indications	Initial dosage will vary from 10 to 500 mg depending on the clinical problem being treated. Larger doses may be required for short-term management of severe, acute conditions as bronchial asthma, serum sickness, urticarial transfusion reactions and acute exacerbations of multiple sclerosis. The initial dose, up to and including 250 mg, should be given intravenously over a period of at least 5 minutes and exceeding 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. Corticosteroid therapy is an adjunct to, and not replacement for, conventional therapy.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.
Medical surveillance is also needed in case of interruption of chronic treatment.
To administer by intravenous (or intramuscular) injection, prepare solution as directed.

Paediatric population
Dosage for children should be based upon the principles of dosing in adults (see above) and should be adjusted based on severity of the condition and clinical response. Treatment should be limited to the minimum dosage necessary to achieve a favourable response and for the shortest period of time. If after long term therapy the medicinal product is to be discontinued, it is advisable to reduce the dose gradually rather than to stop abruptly.
If possible, treatment should be administered as a single dose on alternate days (see section 4.4).

NOTE: Certain methylprednisolone sodium succinate formulations contain benzyl alcohol (see section 4.4 "Paediatric population").

Elderly
Treatment of elderly patients, particularly if long-term, should be planned bearing in mind the potential for more serious consequences of corticosteroids in old age, particularly osteoporosis, diabetes, hypertension, susceptibility to infection and thinning of skin (see section 4.4).

Method of administration
The solution of sodium succinate of methylprednisolone may be administered by intravenous or intramuscular injection or by intravenous infusion. Intravenous injection is preferable for commencing treatment in cases of emergency.

4.3 Contraindications

- Hypersensitivity to methylprednisolone or to any of the excipients listed in section 6.1.
- Solu-Medrol S.A.B. Act-O-Vial 40 mg and Solu-Medrol S.A.B. 40 mg are contraindicated in patients with a known or suspected allergy to cow's milk (see section 4.4).
- Patients with systemic fungal infections.
- Intrathecal route of administration.
- Epidural route of administration.

4.4 Special warnings and precautions for use

Immunosuppressant effects/Increased susceptibility to infections
Glucocorticosteroids may increase susceptibility to infections, may mask some signs of infection and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections due to bacteria, viruses, fungi, protozoa or worms, in any part of the body, may be associated with the use of corticosteroids either alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity or neutrophil action. These infections can be moderate, severe and occasionally fatal. As the corticosteroid dose increases, more infections occur.

Patients treated with immunosuppressive medicinal products 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 treated with corticosteroids.

Administration of live or live attenuated vaccines is not recommended in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines and biogenetic vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the therapeutic reaction to these vaccines may be diminished or even ineffective. Patients on non-immunosuppressive doses of corticosteroids may undergo any required immunization procedures.

Patients under corticosteroid therapy cannot be vaccinated against smallpox. The other vaccinations should be avoided in patients under corticosteroid therapy, especially when used in high doses, due to the potential neurological complications and altered antibody response.

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis, where appropriate anti-tuberculosis regimen is initiated simultaneously. 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 in patients receiving corticosteroid therapy. Discontinuation of corticosteroids 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. One systematic review of short-course, high-dose corticosteroids did not support their use. However, meta-analyses, and one review of the literature suggest that longer courses (5–11 days) of low-dose corticosteroids may reduce mortality, especially in patients with vasopressor-dependent septic shock.

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

Cow's milk allergy (the following paragraphs only apply to Solu-Medrol S.A.B. Act-O-Vial 40 mg and Solu-Medrol S.A.B. 40 mg):
Solu-Medrol S.A.B. Act-O-Vial 40 mg and Solu-Medrol S.A.B. 40 mg contain lactose produced from bovine origin as an excipient and may therefore contain trace amounts of cow's milk proteins (the allergens of cow's milk). Serious allergic reactions, including bronchospasm and anaphylaxis, were reported in patients allergic to cow's milk proteins who were treated for acute allergic conditions. Patients with known or suspected allergy to cow's milk must not be administered Solu-Medrol S.A.B. Act-O-Vial 40 mg and Solu-Medrol S.A.B. 40 mg (see section 4.3).
Allergic reactions to cow's milk proteins should be considered in patients receiving Solu-Medrol S.A.B. Act-O-Vial 40 mg and Solu-Medrol S.A.B. 40 mg for the treatment of acute allergic conditions in whom symptoms worsen or who are presenting new allergic symptoms (see section 4.3).
Administration of Solu-Medrol S.A.B. Act-O-Vial 40 mg and Solu-Medrol S.A.B. 40 mg should be stopped, and the patient's condition should be treated accordingly.

Endocrine effects
In patients treated with corticosteroids subjected to unusual stress, an increased dose of rapidly acting corticosteroids may be required before, during and after the stressful situation.

Pharmacological doses of glucocorticoids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) axis suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy. This effect may be minimised by alternate-day therapy.

In addition, acute adrenal insufficiency with a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

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

Steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuation 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, they should be avoided in patients with this syndrome.

The effect of corticosteroids is enhanced in patients with hypothyroidism.

Metabolism and nutrition
Corticosteroids, including methylprednisolone, may increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus. These patients should be treated while under close medical supervision, and for the shortest period possible.

Psychiatric impacts
Psychiatric disorders ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations may appear during treatment with corticosteroids. Existing emotional and psychotic instability or psychotic tendencies may also be aggravated by corticosteroids.

Potentially severe adverse psychiatric reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover either after dose reduction or withdrawal of the treatment, 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 remarks on myopathy in the section "Musculoskeletal effects" below).

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute episodes in 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 for a significant effect to appear.

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 treated with corticosteroids, typically with long-term use at high doses.

Ocular effects
Corticosteroids should be used with caution in patients with ocular herpes simplex or herpes zoster associated with ocular symptoms due to the risk of 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. Glucocorticoids may also promote the appearance of secondary fungal or viral infections of the eye.

Visual disturbance may be reported with systemic and topical corticosteroids. 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.
Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

Cardiac effects
Side effects of glucocorticoids on the cardiovascular system, such as dyslipidaemia and hypertension, may predispose treated patients with other existing cardiovascular risk factors to additional cardiovascular effects, in case of prolonged high-dose treatment. Accordingly, corticosteroids should be used with caution in such patients. Attention should be paid to changes in lipid profile, and additional cardiac monitoring should be provided if required. Low dose and alternate-day treatment may reduce the incidence of complications.

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

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

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.

Steroids should be used with caution in patients with hypertension, as the risk of increased arterial hypertension is further elevated. These patients should be treated while under close medical supervision, and for the shortest period possible.

Gastrointestinal effects
High doses of corticosteroids may produce acute pancreatitis.

There is no universal consensus regarding the involvement of corticosteroids per se in the appearance peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer, and 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 risk of impending perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary effects
Hepatobiliary effects: drug induced liver injury including acute hepatitis or liver enzyme increase can result from cyclical pulsed intravenous methylprednisolone (usually at initial dose ≥ 1 g/day). Rare cases of hepatotoxicity have been reported. The time to onset can be several weeks or longer. In the majority of case reports resolution of the adverse events has been observed after treatment was discontinued. Therefore, appropriate monitoring is required.

High doses of corticosteroids may cause acute pancreatitis.
The effect of glucocorticoids is more significant in cases of cirrhosis.

Musculoskeletal effects
Acute myopathy has been reported with the use of high corticosteroid doses, usually in patients with disorders of neuromuscular transmission (for example, myasthenia gravis), or in patients receiving concurrent treatment with anticholinergics, such as neuromuscular blockers (for example, pancuronium). This acute myopathy is generalized, can affect eye muscles and respiratory muscles and can result in quadriparesis. Increased creatine kinase levels can occur. After discontinuation of the corticosteroid treatment it may take weeks to years before clinical improvement or recovery occurs.

Osteoporosis is a common but rarely recognised side effect associated with the long-term, high-dose use of glucocorticoids.

Renal and urinary disorders
Corticosteroids should be used with caution in patients with renal impairment.

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

Investigations
Average and high 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 at high doses. Dietary salt restriction and potassium supplements may be necessary. All corticosteroids increase calcium excretion.

Treatment with corticosteroids must be taken into consideration when interpreting certain biological tests (particularly skin tests, thyroid hormone levels).

Injury, poisoning and procedural complications
Systemic corticosteroids are not indicated for and therefore should not be used to treat traumatic brain injury. One multicentre study revealed an increased mortality in the 2 weeks and 6 months following trauma in patients administered methylprednisolone sodium succinate compared to placebo (relative risk 1.18). No causal association with methylprednisolone sodium succinate treatment has been established.

Injection in the deltoid muscle should be avoided due to the high risk of subcutaneous atrophy.

Other
Since complications of treatment with glucocorticoids are dependent on the dose and the duration of treatment, the dose, frequency and duration of administration (daily or alternate-day), a decision must be made in each individual case, taking into consideration the risks and benefits.

The lowest possible dose of corticosteroids should be used to control the condition under treatment, when a dose reduction is possible, the reduction should be gradual.

The duration of treatment should in general be kept as short as possible. Medical surveillance is recommended during chronic treatment (see section 4.2). The gradual discontinuation of chronic treatment should also take place under medical surveillance (gradual dose reduction, evaluation of adrenocortical function). The most important symptoms of adrenocortical insufficiency are asthenia, orthostatic hypotension and depression.

Acetylsalicylic acid and nonsteroidal anti-inflammatory agents should be used with caution in combination with corticosteroids.

An attack of pheochromocytoma, which can be fatal, was reported after administration of systemic corticosteroids. Corticosteroids may only be administered to patients with suspected or identified pheochromocytoma after an appropriate assessment of benefits/risks.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects (see section 4.5).

Solu-Medrol S.A.B. Act-O-Vial 40 mg and 125 mg Powder and solvent for solution for injection and Solu-Medrol S.A.B. 40 mg and 125 mg Powder and solvent for solution for injection contain less than 1 mmol sodium (23 mg) per vial or Act-O-Vial, that is to say essentially 'sodium-free'.

Solu-Medrol S.A.B. Act-O-Vial 250 mg Powder and solvent for solution for injection contains 32.56 mg sodium per Act-O-Vial.
Solu-Medrol 500 mg and 500 mg S.A.B. 40 mg Powder and solvent for solution for injection contains 58.39 mg sodium per vial.
Solu-Medrol 1000 mg and 1000 mg S.A.B. 40 mg Powder and solvent for solution for injection contains 116.78 mg sodium per vial.
This should be taken into account for the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population
Some of these preparations contain benzyl alcohol. Reconstituted solutions of Solu-Medrol contain 9 mg benzyl alcohol per ml.
Reconstituted solutions of Solu-Medrol S.A.B. and S.A.B. Act-O-Vial do not contain benzyl alcohol. Benzyl alcohol may cause hypotension in children. Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Benzyl alcohol must not be given to a newborn baby (up to 4 weeks old), unless recommended by the doctor. Due to increased risk due to accumulation, benzyl alcohol must not be used in children not used for more than a week in young children (less than 3 years old), unless advised by the doctor or pharmacist. High volumes should be used with caution and only if necessary, especially in pregnant or breast-feeding women or in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored. Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and this regimen should be restricted to the most urgent indications. Alternate-day glucocorticoid therapy usually avoids or minimises this side effect.

Infants and children treated with corticosteroids in the long term are at particular risk of increased intracranial pressure.

High doses of corticosteroids may cause pancreatitis in children.

Cases of transient myocardial hypertrophy have been reported in premature neonates receiving corticosteroid therapy for lung diseases.

Children should be treated while under close medical supervision, and for the shortest period possible.

4.5 Interaction with other medicinal products and other forms of interaction

Methylprednisolone is a cytochrome P450 (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 compounds are also substrates of CYP3A4, some of which (along with other medicinal products) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS – Medicinal products that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity.
CYP3A4 INDUCERS – Medicinal products that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medicinal products that are substrates for CYP3A4. Co-administration may require a dose increase of methylprednisolone to achieve the desired result.
CYP3A4 SUBSTRATES - In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, and corresponding dose adjustments may therefore be required. It is possible that adverse events associated with the use of either medicinal product alone may be more likely to occur with co-administration.
EFFECTS NOT MEDIATED BY CYP3A4 – Other interactions and effects that occur with methylprednisolone are described in the table below. The table provides a list and descriptions of the most common and/or clinically important drug interactions or effects with methylprednisolone.

Important drug or substance interactions/effects with methylprednisolone

Medicinal product class or type - MEDICINAL PRODUCT or SUBSTANCE	Interaction/Effect
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone increasing the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There have been reports of enhanced as well as diminished effects of anticoagulants when administered concomitantly with corticosteroids. Coagulation indices should therefore be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKING AGENTS	Corticosteroids may influence the effect of anticholinergics. 1) Acute myopathy has been reported with concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking agents (for more information, see section 4.4 "Musculoskeletal effects"); 2) Antagonism of the neuromuscular blocking effects induced by pancuronium and vecuronium has been reported in patients using corticosteroids. This interaction may occur with all competitive neuromuscular blocking agents.
Anticholinesterases	Steroids may reduce the effect of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dose adjustments of antidiabetic agents may be required.
Antiemetics - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors and thus reduce their plasma concentrations.
Pharmacokinetic enhancers - COBICISTAT	CYP3A4 INHIBITORS Pharmacokinetic enhancers inhibit CYP3A4 activity leading to a decreased hepatic clearance and increased plasma concentration of corticosteroids. A dose adjustment of the corticosteroid may be required (see section 4.4).
Aromatase inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenocortical suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium channel blockers - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Contraceptives (oral) - ETHINYLESTRADIOL/ - NORETHISTERONE - GRAPEFRUIT JUICE	CYP3A4 INHIBITOR (and SUBSTRATE) CYP3A4 INHIBITOR
Immunosuppressants - CICLOSPORIN	CYP3A4 INHIBITOR (and SUBSTRATE) 1) Mutual inhibition of metabolism occurs with concurrent use of ciclosporin and methylprednisolone, which may increase the plasma concentrations of either or both substances. It is possible that side effects associated with the use of either alone may be more likely to occur upon coadministration. 2) Convulsions have been reported with concomitant use of methylprednisolone and ciclosporin.
Immunosuppressants - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide antibacterials - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
Macrolide antibacterials - TROLEANDOMYCIN	CYP3A4 INHIBITOR
NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose acetylsalicylic acid	1) There may be an increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are administered with NSAIDs. 2) Methylprednisolone may increase the clearance of high-dose acetylsalicylic acid. This can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which may result in an increased risk of salicylate toxicity. 3) Acetylsalicylic acid should be used with caution in combination with corticosteroids in hypoprothrombinaemia.
Potassium depleting agents	When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., diuretics), patients should be closely monitored for potential development of hypokalaemia. The combination of glucocorticoids with thiazide-diuretics increases the risk of glucose intolerance.
Incompatibilities	There is also an increased risk of hypokalaemia where corticosteroids are used concomitantly with amphotericin B, xanthines, or beta2 mimetics.

To avoid compatibility and stability problems, it is recommended to administer methylprednisolone sodium succinate separately from other compounds administered via the IV route. Medicinal products physically incompatible in solution with methylprednisolone sodium succinate include, but are not limited to: allopurinol sodium, doxapram hydrochloride, figecycline, diltiazem hydrochloride, calcium gluconate, vecuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol (see section 6.2).

DESIRED INTERACTIONS
In treatment of neoplastic disease such as leukaemia and lymphoma, methylprednisolone is usually used in combination with alkylating agents, antimetabolites and vinca alkaloids.

4.6 Fertility, pregnancy and lactation

Pregnancy
Some animal studies have shown that corticosteroids when administered during pregnancy at high doses, may cause foetal malformations (see section 5.3).
Administration of corticosteroids in pregnant women however does not appear to induce congenital anomalies. In the absence of adequate studies of the effects of methylprednisolone sodium succinate on human reproduction, this medicinal product should only be used during pregnancy following careful evaluation of the ratio of benefits to risks for the mother and the foetus. If a chronic treatment with corticosteroids has to be stopped during pregnancy (as with other chronic treatments), this should occur gradually (see section 4.2). In some cases (e.g. substitution treatment of adrenocortical insufficiency) however, it can be necessary to continue treatment or even to increase dosage.
Some corticosteroids readily cross the placenta. One retrospective study revealed an increased incidence of low-birth weight in infants born to mothers treated with corticosteroids. In humans, the risk of low birth weight seems dose-dependent and can be reduced by administering lower doses of corticosteroids. Though neonatal adrenocortical insufficiency is rare in infants who were exposed *in utero* to corticosteroids, infants who were exposed to substantial doses of corticosteroids should be carefully observed and evaluated for signs of adrenocortical insufficiency.

Cases of cataracts have been observed in infants born to mothers having received prolonged treatment with corticosteroids during pregnancy.

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

Benzyl alcohol can cross the placenta (see section 4.4). This warning does not apply to Solu-Medrol S.A.B. (without benzyl alcohol).

Lactation
Corticosteroids are excreted in breast milk.

Corticosteroids are teratogenic in many animal species at administration of doses equivalent to the ones used in humans. In animal reproduction studies, glucocorticoids such as methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-foetal demise (such as an increase in reabsorption) and intra-uterine growth retardation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder and solvent for solution for injection (without benzyl alcohol):
Act-O-Vial system:
- Solu-Medrol S.A.B. (= Sine Alcohol Benzylicus) Act-O-Vial 40 mg Powder and solvent for solution for injection: lactose, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, Sodium Hydroxide, water for injection
- Solu-Medrol S.A.B. (= Sine Alcohol Benzylicus) Act-O-Vial 125 mg – 250 mg Powder and solvent for solution for injection: monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, Sodium Hydroxide, water for injection

Powder and solvent for solution for injection:
- Solu-Medrol 500 mg – 1000 mg - Powder and solvent for solution for injection:
  - Powder: monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, Sodium Hydroxide.
  - Solvent: benzyl alcohol, water for injection.

Powder and solvent for solution for injection (without benzyl alcohol):
- Solu-Medrol S.A.B. (= Sine Alcohol Benzylicus) 40 mg Powder and solvent for solution for injection:
  - Powder: lactose, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous.
  - Solvent: water for injection
- Solu-Medrol S.A.B. (= Sine Alcohol Benzylicus) 125 mg – 500 mg – 1000 mg - Powder and solvent for solution for injection:
  - Powder: monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous
  - Solvent: water for injection

6.2 Incompatibilities

Intravenous compatibility and stability of methylprednisolone sodium succinate solutions and with other drugs in intravenous admixtures are dependent on admixture pH, concentration, time, temperature and the ability of methylprednisolone to solubilize itself. Thus, to avoid compatibility and stability problems, whenever possible it is recommended that solutions of methylprednisolone sodium succinate be administered separate from other drugs and as either intravenous push, through and intravenous medication chamber or as an intravenous "piggy-back" solution (see section 4.5 for more information).

6.3 Shelf life

Do not use Solu Medrol after the expiry date which is stated on the carton / vial label after **"EXP:".** The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Un-reconstituted product:
- Act-O-Vial presentations: Do not store above 30°C.
- Solu-Medrol S.A.B. 40 mg Powder and solvent for solution for injection (vial): Do not store above 30°C.
- Other vial presentations: Do not store above 30°C. .

After reconstitution :
Chemical and physical in-use stability of the reconstituted product has been demonstrated for a period of 12 hours at 25°C.
From a microbiological point of view, unless the method of opening/ reconstitution/dilution excludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.5 Nature and content of container

Solu-Medrol S.A.B. Act-O-Vial 40 mg Powder and solvent for solution for injection: 1 and 3 Act-O-Vials.
Solu-Medrol S.A.B. Act-O-Vial 125 mg Powder and solvent for solution for injection: 1 Act-O-Vial
Solu-Medrol S.A.B. Act-O-Vial 250 mg Powder and solvent for solution for injection: 1 Act-O-Vial.
Solu-Medrol 500 mg Powder and solvent for solution for injection:
1 vial + 1 vial.
Solu-Medrol 1000mg Powder and solvent for solution for injection:
1 vial + 1 vial.
Solu-Medrol S.A.B. 40 mg Powder and solvent for solution for injection: 1 vial + 1 ampoule and 3 vials + 3 ampoules.
Solu-Medrol S.A.B. 125 mg Powder and solvent for solution for injection: 1 vial + 1 ampoule.
Solu-Medrol S.A.B. 500 mg Powder and solvent for solution for injection: 1 vial + 1 vial.
Solu-Medrol S.A.B. 1000 mg Powder and solvent for solution for injection: 1 vial + 1 vial.
Not all pack sizes or strengths may be marketed

6.6 Special precautions for disposal and other handling

Keep out of sight and reach of children.

DIRECTIONS FOR USE OF THE ACT-O-VIAL
1. Press down the plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic covering center of stopper.
4. Sterilize top of stopper with a suitable germicide.

Note: steps 1-4 must be completed before proceeding.

5. Insert needle, preferably a 22G, **vertically through center** of stopper until tip is just visible. Turn the vial and draw up the required dose. If a filter needle is used, it is important to avoid to turn the needle and to insert it perpendicularly to the center of rubber stopper.

Specific populations

Sex
The clearance of methylprednisolone was higher in healthy women than in healthy men after intravenous administration of a single dose: 0.45 versus 0.29 l/h/kg. There were nonetheless no differences in pharmacodynamic measures.

Elderly
Methylprednisolone clearance in healthy elderly men (69–82 years) was lower than in younger men (24–37 years) after intravenous administration of a single dose: 0.24 *versus* 0.36 l/h/kg.

*Pa