Solu-Medrol®

Methylprednisolone Sodium Succinate

Act-O-Vial 40 mg – Powder and solvent for solution for injection

Act-O-Vial 125 mg – Powder and solvent for solution for injection

500 mg Powder and solvent for solution for injection

Reference Market: Belgium

AfME markets using the same as LPD: Kenya, Uganda

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Solu-Medrol S.A.B. (= Sine Alcohol Benzylicus) Act-O-Vial 40 mg – Powder and solvent for solution for injection
Solu-Medrol S.A.B. (= Sine Alcohol Benzylicus) Act-O-Vial 125 mg – Powder and solvent for solution for injection
Solu-Medrol 500 mg Powder and solvent for solution for injection

(methylprednisolone)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of Solu-Medrol is methylprednisolone. It is present in the form of methylprednisolone sodium succinate.

Powder and solvent for solution for injection (without benzyl alcohol) :Act-O-Vial system:
Solu-Medrol S.A.B. Act-O-Vial 40 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone

Solu-Medrol S.A.B. Act-O-Vial 125 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone

Powder and solvent for solution for injection:
Solu-Medrol 500 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone

Excipients with known effect:
Benzyl alcohol: Reconstituted solutions of Solu-Medrol, containing 9 mg of benzyl alcohol per ml, with the exception of reconstituted solutions of Solu-Medrol S.A.B. Act-O-Vial (without benzyl alcohol).

Sodium:
- Solu-Medrol S.A.B. Act-O-Vial 40 mg Powder and solvent for solution for injection contains 11.27 mg sodium per Act-O-Vial.
- Solu-Medrol S.A.B. Act-O-Vial 125 mg Powder and solvent for solution for injection contains 16.52 mg sodium per Act-O-Vial.
- Solu-Medrol 500 mg Powder and solvent for solution for injection contains 58.39 mg sodium per vial.

Lactose: Reconstituted solutions of Solu-Medrol S.A.B. Act-O-Vial 40 mg Powder and solvent for solution for injection containing 25 mg of lactose per ml.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Each package contains a sterile powder for injection and a sterile solution.
Intravenous and intramuscular administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glucocorticoids should only be considered as a purely symptomatic treatment, unless in case of some endocrine disorders, where they are used as substitution treatment.

Anti-inflammatory treatment

- *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 nonspecific tenosynovitis
  - 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
  - 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
  - Berylliosis
  - 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 thrombocytopenica purpura in adults (intravenous only; intramuscular administration is contraindicated)
  - Secondary thrombocytopenia in adults
  - Erythroblastopenia (R.B.C. 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
- Acute adrenocortical insufficiency

For these indications, the drugs of choice are hydrocortisone or cortisone. Synthetic analogues can be used in certain circumstances if they are combined with mineralocorticoids.

- Treatment of shock conditions: shock resulting from adrenocortical insufficiency or shock that does not respond to conventional treatment, in the case of confirmed or suspected adrenocortical insufficiency (in general, hydrocortisone is the preparation of choice. If mineralocorticoid effects are undesired, preference can be given to methylprednisolone).
- Prior to surgical procedures and in the case of severe disease or injury, in patients with known adrenocortical insufficiency or doubtful adrenal reserves.
- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis
- Hypercalcaemia associated with cancer

4.2 Posology and method of administration

Posology

Dosage requirements are variable and must be individualized on the basis of the disease under treatment, its severity and the response of the patient over the entire duration of treatment. A risk/benefit decision must be made in each individual case on an ongoing basis.

The lowest possible dose of corticosteroid should be used to control the condition under treatment for the minimum period. The proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage, which will maintain an adequate clinical response, is reached.

If after long-term therapy the drug is to be stopped, it needs to be withdrawn gradually rather than abruptly (see section 4.4).
Medical surveillance is also needed in case of interruption of chronic treatment. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued.

Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

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

Indication	Recommended posology of methylprednisolone sodium succinate
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).
Methylprednisolone IV pulses	Administration of 250 mg/day or above for a few days (usually ≤ 5 days) may be suitable during exacerbation episodes or conditions unresponsive to standard therapy, such as: rheumatic disorders, systemic lupus erythematosus, oedematous states, such as lupus nephritis (see section 4.4). In general, when determining the appropriate dose for systemic lupus erythematosus and rheumatic diseases, the healthcare professional should consider guideline recommendations, clinical judgement and patient factors. As high doses of corticosteroids can cause an arythmogenic action, this therapy should be restricted to hospitals, which dispose of an electrocardiograph and defibrillator.
Multiple sclerosis unresponsive to standard therapy (or during exacerbation episodes)	Administer pulses of 500 or 1000 mg/day for 3 or 5 days over a period of at least 30 minutes.
Adjunctive therapy in other conditions	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 and urticarial transfusion reactions. The initial dose, up to and including 250 mg, should be given intravenously over a period of at least 5 minutes and doses 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.
Prevention of nausea and vomiting associated with cancer chemotherapy	In deciding the optimal dosing strategy for prevention of nausea and vomiting associated with cancer chemotherapy, the healthcare professional

	may align with the local therapeutic guidelines and institutional practices, where applicable.
Acute spinal cord injury	**The treatment should begin within eight hours of injury.** In deciding the optimal dosing strategy for the patient with acute spinal cord injury, the healthcare professional may align with the local therapeutic guidelines and institutional practices, where applicable. (see section 5.1)

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
For intravenous or intramuscular injection or by intravenous infusion via an infusion pump (see sections 6.2 and 6.6), the solution must be prepared according to the instructions. 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.
- Patients with systemic fungal infections
- Solu-Medrol S.A.B. Act-O-Vial 40 mg is contraindicated in patients with a known or suspected allergy to cow’s milk (see section 4.4).
- Intrathecal route of administration.
- Epidural route of administration.

4.4 Special warnings and precautions for use

General
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 and, 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 discontinuation, evaluation of adrenocortical function). The most important symptoms of adrenocortical insufficiency are asthenia, orthostatic hypotension and depression.

During long-term treatments, regular chest X-rays and routine laboratory tests such as urinalysis, blood glucose two hours after eating, blood pressure and body weight are recommended. In patients with a gastric ulcer or severe dyspepsia, an X-ray of the upper gastrointestinal tract is recommended.

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. The use of methylprednisolone pulses, 1000 mg/day for 3 days have been shown to be associated with an increase in infections **c**ompared with 500 mg/day. Thus, the use of maintenance doses of prednisone not exceeding 5 mg/day with pulses of 500 mg of methylprednisolone instead of 1000 mg is probably a good way to reduce the infectious complications in lupus patients.

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 immunisation 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 immune 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):

Solu-Medrol S.A.B. Act-O-Vial 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 (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 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 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.

Thyrotoxic Periodic Paralysis (TPP) can occur in patients with hyperthyroidism and with methylprednisolone-induced hypokalaemia. TPP must be suspected in patients treated with methylprednisolone presenting signs or symptoms of muscle weakness, especially in patients with hyperthyroidism. If TPP is suspected, levels of blood potassium must be immediately monitored and adequately managed to ensure the restoration of normal levels of blood potassium.

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 effects
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 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 after either 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 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.
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 risk, 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 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. 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
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).

In post marketing experience tumor lysis syndrome (TLS) has been reported in patients with malignancies, including hematological malignancies and solid tumors, following the use of systemic corticosteroids alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumors that have a high proliferative rate, high tumor burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

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

Solu-Medrol 500 mg Powder and solvent for solution for injection contains 58.39 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 presentations contain benzyl alcohol. Reconstituted solutions of Solu-Medrol contain 9 mg benzyl alcohol per ml. Reconstituted solutions of Solu-Medrol S.A.B. Act-O-Vial do not contain benzyl alcohol. Benzyl alcohol may cause allergic reactions. 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 in young children, benzyl alcohol must not be 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.

Hypertrophic cardiomyopathy may develop after administration of methylprednisolone to prematurely born infants. Also, cases of transient myocardial hypertrophy have been reported in premature neonates receiving corticosteroid therapy for lung diseases. Therefore, appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

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 an 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 taking corticosteroids. This interaction may occur with all competitive neuromuscular blocking agents.
Anticholinesterases	Steroids may reduce the effects 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 adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium channel blockers - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)

Medicinal product class or type **- MEDICINAL PRODUCT or SUBSTANCE**	**Interaction/Effect**
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHISTERONE	CYP3A4 INHIBITOR (and SUBSTRATE)
- GRAPEFRUIT JUICE	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, which 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. There is also an increased risk of hypokalaemia where corticosteroids are used concomitantly with amphotericin B, xanthenes, or beta2 mimetics.

Incompatibilities

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, tigecycline, 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 in breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. This medicinal product should only be used while breastfeeding following careful evaluation of the ratio of benefits to risks for the mother and the infant.

Fertility
Corticosteroids have been shown to impair fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Solu-Medrol has a minor influence on the ability to drive and use machines. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or use machines.

4.8 Undesirable effects

Safety profile summary
The following undesirable side effects are typical of methylprednisolone sodium succinate. Hypersensitivity reactions may occur at the start of treatment (see section 4.4). Serious infections, including opportunistic infections, may also occur during treatment with corticosteroids. Other side effects include: convulsions, pathological fractures and vertebral settlement fractures, gastric ulcers with perforation or haemorrhage, torn tendons, psychiatric disorders or manifestations, Cushing's

syndrome, steroid withdrawal syndrome, hypertension, myopathy, glaucoma, subcapsular cataract, decreased glucose tolerance, rash, fluid retention, abdominal pain, nausea, headaches and dizziness.

The following side effects have been reported with the following contraindicated routes of administration: intrathecal/epidural: arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparisis/paraplegia, convulsions, sensory disturbances. The frequency of these side effects is not known.

Table of side effects

System organ class MedDRA	Frequency not known (cannot be estimated from the available data)
Infections and infestations	Infection; opportunistic infection, peritonitis*.
Blood and lymphatic system disorders	Leukocytosis.
Immune system disorders	Drug hypersensitivity (including anaphylactic and anaphylactoid reactions).
Endocrine disorders	Cushing syndrome, hypothalamic pituitary adrenal axis suppression, steroid withdrawal syndrome.
Metabolism and nutrition disorders	Metabolic acidosis, lipomatosis, sodium retention, fluid retention, hypokalaemic alkalosis, dyslipidaemia, impaired glucose tolerance, increased insulin requirements (or oral hypoglycaemic agents in diabetics), increased appetite (which may result in weight gain).
Psychiatric disorders	Affective disorders (including depressed mood, euphoria, affect lability, pharmacological dependence, suicidal ideation), psychotic disorders (including mania, delusion, hallucination, and schizophrenia), mental disorders, personality change, confusional state, anxiety, mood swings, abnormal behaviour, insomnia, irritability.
Nervous system disorders	Epidural lipomatosis, increased intracranial pressure (with papilloedema [benign intracranial hypertension]), convulsions, amnesia, cognitive disorder, dizziness, headache.
Eye disorders	Chorioretinopathy, cataract, glaucoma (with potential optic nerve lesions), exophthalmos, vision blurred (see section 4.4).
Ear and labyrinth disorders	Vertigo.
Cardiac disorders	Congestive heart failure (in predisposed patients), arrhythmia, myocardial rupture following myocardial infarction. Cases of cardiac arrhythmia and/or circulatory collapse and/or cardiac arrest have been reported upon rapid intravenous administration of high doses of methylprednisolone sodium succinate (more than 0.5 g in less than 10 minutes). Bradycardia has been observed during or after administration of high doses of methylprednisolone sodium succinate, which may also occur regardless of the rate or duration of infusion. Tachycardia has been reported after administration of high doses of glucocorticoids.
Vascular disorders	Thrombotic events, hypertension, hypotension, flushing.

System organ class MedDRA	Frequency not known (cannot be estimated from the available data)
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, hiccups.
Gastrointestinal disorders	Peptic ulcer (with risk of perforation and haemorrhage), intestinal perforation, gastric haemorrhage, pancreatitis, ulcerative oesophagitis, oesophagitis, abdominal distention, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting.
Hepatobiliary disorders	Hepatitis†, elevated liver enzymes (for example AST, ALT).
Skin and subcutaneous tissue disorders	Angioedema, hirsutism, petechiae, ecchymosis, skin atrophy, erythema, hyperhidrosis, skin striae, rash, pruritus, urticaria, acne, skin hypopigmentation, panniculitisβ. Local atrophy may be observed at the site of injection in case of repeated subcutaneous injections.
Musculoskeletal and connective tissue disorders	Muscular weakness, myalgia, myopathy, muscular atrophy, osteoporosis, osteonecrosis, pathological fracture, neuropathic arthropathy, arthralgia, growth retardation.
Reproductive system and breast disorders	Irregular menstruation.
General disorders and administration site conditions	Peripheral oedema, impaired healing, fatigue, malaise, injection site reactions.
Investigations	Increased urine calcium, decreased blood potassium, increased intraocular pressure, decreased carbohydrate tolerance, increased blood urea, increased alanine aminotransferase; increased aspartate aminotransferase; increased blood alkaline phosphatase; suppression of reactions to skin tests.
Injury, poisoning and procedural complications	Spinal compression fracture, tendon rupture.

* Peritonitis may be the main sign or symptom of the onset of a gastrointestinal disorder, such as perforation, obstruction or pancreatitis (see section 4.4).
† Hepatitis has been reported with intravenous administration (see section 4.4).
β Few cases of panniculitis have been reported following dose reduction or discontinuation of therapy, especially after long-term, high-dose treatment. Panniculitis is more common in paediatric patients than in adults, and most cases resolve spontaneously.

Paediatric population
The frequency, type and severity of undesirable effects in children are expected to be the same as in adults.

Growth may be suppressed in children receiving long-term glucocorticoid therapy (see section 4.4).

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after marketing of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local requirements.

4.9 Overdose

Symptoms

There is no clinical syndrome of acute overdose with corticosteroids.
Reports of acute toxicity and/or death following overdose of corticosteroids are rare. Chronic overdose induces typical Cushing-type symptoms.

Treatment
There is no specific antidote in case of overdose; symptomatic support should be started.
Methylprednisolone is dialysable.

5. PHARMACOLOGICAL PROPERTIES

This product is an intramuscular and intravenous injectable form of methylprednisolone, a synthetic glucocorticosteroid. This highly concentrated aqueous solution is particularly suitable for the treatment of pathologic conditions, in which an effective and rapid hormonal effect is required.
Methylprednisolone has a strong anti-inflammatory, immunosuppressive and anti-allergic activity.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : glucocorticosteroid, ATC H02AB04

Glucocorticoids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin), and stimulate transcription of mRNA and subsequent protein synthesis of various enzymes thought to be ultimately responsible for the numerous effects of glucocorticoids after systemic use. Glucocorticoids not only have an important influence on inflammatory and immune processes, but also affect the carbohydrate, protein and fat metabolism. They also act on the cardiovascular system, the skeletal muscles and the central nervous system.

- Effect on the inflammatory and immune process:
  The anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids are responsible for most of the therapeutic applications. These properties lead to the following results:
  - reduction of the immunoactive cells near the inflammation focus;
  - reduced vasodilation;
  - stabilization of the lysosomal membranes;
  - inhibition of phagocytosis;
  - reduced production of prostaglandines and related substances.

  A dose of 4 mg methylprednisolone has the same glucocorticosteroid (anti-inflammatory) effect as 20 mg hydrocortisone. Methylprednisolone has only a minimal mineralocorticoid effect (200 mg methylprednisolone are equivalent to 1 mg desoxycorticosterone).
- Effect on carbohydrate and protein metabolism:
  Glucocorticoids have a protein catabolic action. The liberated amino acids are converted into glucose and glycogen in the liver by means of the gluconeogenesis process. Glucose absorption in peripheral tissues decreases, which can lead to hyperglycemia and glucosuremia, especially in patients who are prone to diabetes.
- Effect on fat metabolism:
  Glucocorticoids have a lipolytic action. This lipolytic activity mainly affects the limbs. They also have a lipogenetic effect which is most evident on chest, neck and head. All this leads to a redistribution of the fat deposits.

Maximum pharmacologic activity of corticosteroids lags behind peak blood levels, suggesting that most effects of the drugs result from modification of enzyme activity rather than from direct actions by the drugs.

Methylprednisolone sodium succinate has been investigated for acute spinal cord injury in two randomized, double-blind, comparative National Acute Spinal Cord Injury Studies (NASCIS 2 and 3). The effect of high dose methylprednisolone sodium succinate given as initial bolus of 30 mg/kg by IV

for 15 minutes followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hour for 24 hours was significant on neurologic recovery when given to patients within 8 hours from injury (NASCIS 2) and motor recovery was higher for those patients initiated within 3 to 8 hours from injury and treated with the same regimen for 48 hours (NASCIS 3).

5.2 Pharmacokinetic properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Absorption
In vivo, cholinesterases rapidly hydrolyze methylprednisolone sodium succinate to free methylprednisolone.
In man, methylprednisolone forms a weak dissociable bond with albumin and transcortin. Approximately 40 to 90% of the drug is bound.
Intravenous infusions with 30 mg/kg, administered over 20 minutes or 1 g administered over 30 to 60 minutes lead after approximately 15 minutes to peak methylprednisolone plasma levels of nearly 20 µg/ml. About 25 minutes after an intravenous bolus injection of 40 mg peak methylprednisolone plasma values of 42-47 µg/100 ml are measured. Intramuscular injections of 40 mg give peak methylprednisolone plasma levels of 34 µg/100 ml after some 120 minutes. Intramuscular injections give lower peak values than intravenous injections. With intramuscular injections plasma values persist for a longer period, with the result that both administration patterns lead to equivalent quantities of methylprednisolone. The clinical importance of these small differences is probably minimal when we consider the mechanism of action of glucocorticoids.
A clinical response is usually observed 4 to 6 hours after administration. In the treatment of asthma, the first beneficial results can already be perceived after 1 or 2 hours. The plasma half-life of methylprednisolone sodium succinate is 2.3 to 4 hours and appears to bear no relation to the administration pattern.
Methylprednisolone is a glucocorticoid with a medium-term activity. It has a biological half-life of 12 to 36 hours. The intracellular activity of glucocorticoids results in a clear difference between plasma half-life and pharmacological half-life. Pharmacological activity persists after measurable plasma levels have disappeared. The duration of anti-inflammatory activity of glucocorticoids approximately equals the duration of hypothalamic-pituitary-adrenal (HPA) axis suppression.
Following intravenous administration of C^{14} labelled methylprednisolone, 75% of the total radioactivity was recovered in the urine in 96 hours, 9% was recovered in human faeces after 5 days and 20% in the bile.

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

Biotransformation
Methylprednisolone is metabolised in the liver in a manner qualitatively similar to cortisol. The metabolites are mainly excreted in the urine as glucuronides, sulfates and unconjugated compounds.

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

Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for p-glycoprotein, a protein in the ATP-binding cassette (ABC) transport protein family, which influences tissue distribution and interactions with other medicinal products.

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.

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.

Paediatric population
The clearance of methylprednisolone is mildly related to age. Younger subjects tend to metabolise methylprednisolone more rapidly. In a study of intravenous administration of a single dose in 14 patients with nephrotic syndrome, younger subjects (<13 years) showed greater clearance than the older group (>13 years): 0.53 *versus* 0.38 l/h/kg.

Renal impairment
In a single-dose intravenous study in 6 male subjects with chronic renal impairment, the pharmacokinetics of methylprednisolone remained unchanged compared to healthy controls, with an average clearance of 0.28 l/h/kg. In addition, no differences in pharmacodynamic measures were observed in these subjects with chronic renal failure.

Hepatic impairment
In a single-dose intravenous study in 6 male subjects with chronic liver disease, the pharmacokinetics of methylprednisolone were similar to those in healthy controls, with an average clearance of 0.29 l/h/kg.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, and repeated- dose toxicity no unexpected hazards were identified. The toxicities seen in the repeated-dose studies are those expected to occur with continued exposure to exogenous corticosteroids.

Carcinogenic potential
Methylprednisolone has not been formally evaluated in carcinogenicity studies on rodents. Other glucocorticoids have been tested for carcinogenicity on mice and rats with variable results. However, published data indicates that several similar glucocorticoids, in particular, budesonide, prednisolone and triamcinolone acetonide, may increase the incidence of adenomas and hepatocellular carcinomas after oral administration in the drinking water of male rats. These carcinogenic effects occurred at doses lower than the usual clinical doses expressed in mg/m^2.

Mutagenic potential
There was no evidence of a potential for genetic or chromosome mutations in limited studies in bacterial and mammalian cells.

Reproductive toxicity
Corticosteroids administered to male rats have been shown to reduce fertility. In rats, corticosterone induced a reduction in seminal plugs, the number of implantations and viable foetuses.

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 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 - Powder and solvent for solution for injection :
  - Powder: monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, sodium hydroxide.
  - Solvent: benzyl alcohol, 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 an 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

Solu-Medrol S.A.B. Act-O-Vial 40 mg Powder and solvent for solution for injection:
Store below 30°C.

Solu-Medrol S.A.B. Act-O-Vial 125 mg Powder and solvent for solution for injection:
Store below 30°C.

<u>After reconstitution with solvent:</u>
Chemical and physical in-use stability of the reconstituted product has been demonstrated for a period of 48 hours at 2° - 8°C.

Solu-Medrol 500 mg Powder for solvent for solution for injection:
Store below 25°C.

<u>After reconstitution with solvent:</u>

Chemical and physical in-use stability of the reconstituted product has been demonstrated for a period of 48 hours at 2° - 8°C.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes 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 Act-O-Vial.
Solu-Medrol S.A.B. Act-O-Vial 125 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.

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 on 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 musts 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 thicker needle is used, it is important to avoid to turn the needle and to insert it perpendicularly to the center of rubber stopper.

DIRECTIONS FOR USE OF THE VIAL
Under aseptic conditions add the diluent to the vial with sterile powder. Do only use the special diluent.
To withdraw the dose from the vial, please refer to point 5 “Directions for use of the Act-O-Vial” regarding the size of the needle to be preferably used.

PREPARATION OF PERFUSION SOLUTIONS
First reconstitute the solution as directed. Therapy may be initiated by administering the methylprednisolone sodium succinate solution intravenously over a period of at least 5 minutes (e.g. doses up to and including 250 mg) to at least 30 minutes (e.g. doses exceeding 250 mg). Subsequent doses may be withdrawn and administered similarly. If desired, the medication may be administered in dilute solutions by admixing the reconstituted product with dextrose 5% in water, normal saline, dextrose 5% in 0,45% or 0,9% sodium chloride. The resulting solutions are physically and chemically stable for 48 hours.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer S.A., 17 Boulevard de la Plaine, 1050 Brussels - Belgium

MANUFACTURED BY

Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs-Sint-Amands, Belgium.

8. PRESCRIPTION STATUS

Prescription only medicine

9. DATE OF REVISION OF THE TEXT

May 2026