Solu-Medrol®

Methylprednisolone Sodium Succinate

40 mg – 125 mg – 250 mg Solution for injection

500 mg – 1000 mg – 2000 mg Powder and solvent for solution for injection

40 mg – 125 mg - 500 mg – 1000 mg – 2000 mg Powder and solvent for solution for injection

Belgium

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Solu-Medrol 40 mg – 125 mg – 250 mg Powder and solvent for solution for injection
Solu-Medrol 500 mg – 1000 mg – 2000 mg Powder and solvent for solution for injection
Solu-Medrol S.A.B. (= Sine Alcohol Benzylicus) 40 mg – 125 mg - 500 mg – 1000 mg – 2000 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 :Act-O-Vial system:
Solu-Medrol 40 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone

Solu-Medrol 125 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone

Solu-Medrol 250 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 250 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

Solu-Medrol 1000 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 1000 mg methylprednisolone

Solu-Medrol 2000 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 2000 mg methylprednisolone

Powder and solvent for solution for injection (without benzyl alcohol) :
Solu-Medrol S.A.B. 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. 125 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone

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

Solu-Medrol S.A.B. 1000 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 1000 mg methylprednisolone

Solu-Medrol S.A.B. 2000 mg Powder and solvent for solution for injection : each vial contains methylprednisolone sodium succinate equivalent to 2000 mg methylprednisolone

Excipients with known effect:
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 (without benzyl alcohol).

Reconstituted solutions of Solu-Medrol 40 mg Powder and solvent for solution for injection and Solu-Medrol S.A.B. 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
  - 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
  - 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
See table below for recommended dosages.
Table 1: Recommended dosages of methylprednisolone sodium succinate

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 “Special warnings and precautions for use”).
"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 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, then 250 mg intravenous at the initiation of therapy and at time of discharge.
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 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 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 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. 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 may be reduced for infants and children but should be governed more by the severity of the condition and response of the patient than by age or size. It should not be less than 0.5 mg per kg every 24 hours.

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

Systemic fungal infections
Hypersensitivity to methylprednisolone or to any of the excipients listed in section 6.1.
Solu-Medrol 40 mg and Solu-Medrol 40 mg are contraindicated in patients with a known or suspected allergy to cow's milk (see section 4.4).

RELATIVE CONTRA-INDICATIONS
Special risk groups:
Patients belonging to the following special risk groups should be under strict medical surveillance and should be treated during an as short as possible period (see also sections "Special warnings and precautions for use" and "Adverse reactions"): Children, diabetics, hypertensive patients, patients with psychiatric antecedents, certain infectious diseases such as tuberculosis or certain viral diseases such as herpes and herpes zoster associated with ocular symptoms.

4.4 Special warnings and precautions for use

- Special risk groups
  Patients belonging to the following special risk groups should be under strict medical surveillance and should be treated during an as short as possible period.
  - Children: growth may be suppressed in children receiving long-term, daily-divided doses glucocorticoid therapy. The use of such a regimen should be restricted to those most serious indications.
  - Diabetics: manifestations of latent diabetes mellitus or increased requirements for insulin or oral hypoglycemic agents.
  - Hypertensive patients: aggravation of arterial hypertension.
  - Patients with psychiatric antecedents: existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.
- Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.
- In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.
- Glucocorticosteroids 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.
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to these patients; however, the therapeutic reaction to these vaccines may be diminished. Patients on non-immunosuppressive doses of corticosteroids may undergo any required immunisation procedures.
- Data from a clinical study conducted to establish the efficacy of methylprednisolone sodium succinate in septic shock, suggest that a higher mortality occurred in subsets of patients who

entered the study with elevated serum creatinine levels or who developed a secondary infection after therapy began.

- The use of methylprednisolone sodium succinate 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.
- Because rare instances of anaphylactic (e.g. bronchospasm) 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 drug.
- 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. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.
- There is an enhanced effect of glucocorticosteroids on patients with hypothyroidism and in those with cirrhosis.
- Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.
- 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.
- High doses of corticosteroids may produce acute pancreatitis.
- Treatment with a glucocorticoid may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders, such as perforation, obstruction or pancreatitis.
- 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, active or latent gastric or peptic ulcer, renal insufficiency, hypertension, osteoporosis or myasthenia gravis.
- 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.
- Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.
- Hepatobiliary effects: drug induced liver injury including acute hepatitis or liver enzyme increase can result from cyclical pulsed intravenous methylprednisolone (usually at initial dose $\geq$ 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.
- Convulsions have been observed during combined treatment with methylprednisolone and cyclosporine. Since concurrent administration of these two products results in mutual inhibition of metabolism, convulsions and other adverse effects due to the individual use of these products may be more likely to occur.
- 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 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.

- Kaposi's syndrome has been reported in patients receiving corticosteroid treatment. Discontinuation of corticosteroid treatment may result in clinical remission.
- 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.
- Some of these presentations contain benzyl alcohol. Reconstituted solutions of Solu-Medrol contain 9 mg benzyl alcohol per ml. Reconstituted solutions of Solu-Medrol and 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 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).
- Cow's milk allergy (the following paragraphs only apply to Solu-Medrol Act-O-Vial 40 mg and Solu-Medrol 40 mg):
  Solu-Medrol Act-O-Vial 40 mg and Solu-Medrol 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 Act-O-Vial 40 mg and Solu-Medrol 40 mg (see section 4.3).
  Allergic reactions to cow's milk proteins should be considered in patients receiving Solu-Medrol Act-O-Vial 40 mg and Solu-Medrol 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 Act-O-Vial 40 mg and Solu-Medrol 40 mg should be stopped, and the patient's condition should be treated accordingly.
- Corticotherapy has to be considered when interpreting a whole series of biological tests and parameters (e.g. skin tests, thyroid hormone levels).
- The duration of the treatment should in general be kept as short as possible. Medical surveillance is recommended during chronic treatment (see also "Posology and method of administration"). The discontinuation of a chronic treatment should also occur under medical surveillance (gradual discontinuation, evaluation of the adrenocortical function). The most important symptoms of adrenocortical insufficiency are asthenia, orthostatic hypotension and depression.
- Injection into the deltoid muscle should be avoided because of the high incidence of subcutaneous atrophy.
- Methylprednisolone sodium succinate should not be used routinely to treat head injury as demonstrated by the results of a multicenter study. The study results revealed an increased mortality in the 2 weeks after injury in patients administered methylprednisolone sodium succinate compared to placebo (1.18 relative risk). A causal association with methylprednisolone sodium succinate treatment has not been established.
- 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).

4.5 Interaction with other medicinal products and other forms of interaction

DESIRED INTERACTIONS

- Prevention of nausea and vomiting associated with cancer chemotherapy.
  - Mild to moderately emetogenic chemotherapy.
    For an increased effect, a chlorinated phenothiazine may be used with the first dose methylprednisolone (one hour before chemotherapy).
  - Severely emetogenic chemotherapy.
    For an increased effect, metoclopramide or a butyrophenon may be used with the first dose methylprednisolone (one hour before chemotherapy).
- By the treatment of fulminating or disseminated pulmonary tuberculosis and tuberculous meningitis with subarachnoid block or impending block, methylprednisolone is used concurrently with appropriate antituberculous chemotherapy.
- By the treatment of neoplastic diseases like leukemia and lymphoma, methylprednisolone is usually used in conjunction with an alkylating agent, an antimetabolite and a vinca-alkaloid.

UNDESIRED INTERACTIONS

- Combination of glucocorticosteroids with ulcerogenic drugs (e.g. salicylates and NSAIDs) increases the risk of gastrointestinal complications.
- Combination of glucocorticosteroids with thiazide-diuretics increases the risk of glucose intolerance.
- Glucocorticosteroids can increase the requirements for insulin or oral hypoglycemic agents in diabetics.
- While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and lack of antibody response.
- Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Methylprednisolone can increase the clearance of chronic high doses of aspirin. This may result in a drop in salicylate serum levels or an increased risk of salicylate toxicity when the administration of methylprednisolone is discontinued.
- Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Concurrent administration of these agents results in a mutual inhibition of metabolism. Therefore it is possible that convulsions and other adverse events associated with the individual use of either drug may be more apt to occur.
- Drugs that induce hepatic enzymes (such as phenobarbital, phenytoin and rifampicin) can increase the clearance of methylprednisolone. It may be necessary to increase the dosage of methylprednisolone in order to obtain the desired response.
- CYP3A4-inhibitors (such as macrolides, triazole antimycotics and some calcium channel blockers) can inhibit the metabolism of methylprednisolone and therefore reduce its clearance. In order to avoid steroid toxicity the dosage of methylprednisolone should therefore be titrated.
- Protease inhibitors (e.g. ritonavir, indinavir) and pharmacokinetic enhancers (e.g. cobicistat) inhibit CYP3A4 activity leading to a decreased hepatic clearance and increased plasma concentration of the corticosteroid. A dose adjustment of the corticosteroid may be required (see section 4.4).
- The effect of methylprednisolone on oral anticoagulants varies. Both increased and decreased effects of the anticoagulant have been reported when it is combined with corticosteroids. Consequently, coagulation parameters should be monitored in order to achieve the desired anticoagulant effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
Some animal studies have shown that corticosteroids when administered during pregnancy at high doses, may cause fetal malformations. Administration of corticosteroids in pregnant women however does not appear to induce congenital anomalies. Despite the results in animal experiments, the risk of fetal lesions is low when the drug is used during pregnancy. 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 also "Posology and method of administration"). In some cases (e.g. substitution treatment of adrenocortical insufficiency) however, it can be necessary to continue treatment or even to increase dosage.
Corticosteroids readily cross the placenta. One retrospective study revealed an increased incidence in low birth weight in infants whose mothers had received 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. In case of labor and delivery no effects are known.

Lactation
Corticosteroids, including prednisolone, are excreted in breast milk. 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.

4.7 Effects on ability to drive and use machines

Although visual disorders belong to the rare adverse reactions, caution is recommended in patients driving cars and/or using machines.

4.8 Undesirable effects

Systemic adverse reactions may be observed. Although rarely occurring in very short term therapy, they should always be carefully traced. This is part of the follow-up of any corticotherapy, and does not specifically pertain to any particular product. These possible adverse reactions of glucocorticoids like methylprednisolone are:

Infections and infestations : masking of infections, activation of latent infections, opportunistic infections, peritonitis*

Immune system disorders : hypersensitivity reactions (including anaphylaxis, with or without circulatory collapse, cardiac arrest, bronchospasm)

Endocrine disorders : development of Cushingoid state, suppression of the pituitary adrenocortical axis

Metabolism and nutrition disorders : metabolic acidosis, sodium retention, fluid retention, hypokalemic alkalosis, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics. In comparison with cortisone or hydrocortisone, mineralocorticoid effects are less likely to occur with synthetic derivatives as methylprednisolone.

Dietary salt restriction and potassium supplementation may be necessary. Epidural lipomatosis, lipomatosis (frequency unknown).

Blood and lymphatic system disorders: leukocytosis (frequency unknown)

Psychiatric disorders : Psychic derangements ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations.

Nervous system disorders : increased intracranial pressure with papillary edema (pseudotumor cerebri), seizures, vertigo.

Eye disorders : posterior subcapsular cataracts, exophthalmos. Chorioretinopathy, vision, blurred (see also section 4.4) (frequency unknown).
Prolonged use of glucocorticoids may produce, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses. Glucocorticoids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

Cardiac disorders : congestive heart failure in susceptible patients, myocardial rupture after myocardial infarction, arrhythmias.
There are reports or cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large intravenous doses of methylprednisolone sodium succinate (greater than 0,5 gram administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate and may be unrelated to the speed or duration of infusion. After administration of high doses of glucocorticoids, also tachycardia has been reported.

Vascular disorders : hypertension, hypotension, petechiae. Thrombotic events (frequency unknown).

Respiratory, thoracic and mediastinal disorders : persistent hiccups with high corticosteroid doses

Gastrointestinal disorders : peptic ulceration with possible subsequent perforation and hemorrhage, gastric hemorrhage, pancreatitis, esophagitis, intestinal perforation, vomiting.

Hepatobiliary disorders: hepatitis[†], increase of liver enzymes (for example: SGOT, SGPT. The frequency of this effect is unknown).

Skin and subcutaneous tissue disorders : ecchymoses, thin fragile skin. Repeated local subcutaneous injections may cause local cutaneous atrophy.

Musculoskeletal and connective tissue disorders : steroid myopathy, muscle weakness, osteoporosis, aseptic necrosis

Reproductive system and breast disorders : menstrual irregularities

General disorders and administration site conditions : peripheral oedema, impaired wound healing, suppression of growth in children

Investigations : potassium loss, possible transient and moderate increase of alkaline phosphatase levels but it is not associated with any clinical syndrome.Increased intraocular pressure, decreased carbohydrate tolerance, urine calcium increased, blood urea increased, suppression of reactions to skin tests

Injury, poisoning and procedural complications : pathologic fractures, vertebral compression fractures, tendon rupture (mainly the Achilles' tendon)

* 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).

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

There is no clinical syndrome of acute overdosage with methylprednisolone sodium succinate. Chronic overdosage induces typical Cushing symptoms. Methylprednisolone is dialyzable.

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 prostaglandins 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.

5.2 Pharmacokinetic properties

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.
Metabolism of methylprednisolone occurs via hepatic routes qualitatively similar to that of cortisol. The major metabolites are 20 beta-hydroxymethylprednisolone and 20 beta-hydroxy-6 alpha-methylprednisone. The metabolites are mainly excreted in the urine as glucuronides, sulfates and unconjugated compounds.
Following intravenous administration of C14 labeled methylprednisolone, 75% of the total radioactivity was recovered in the urine in 96 hours, 9% was recovered in human feces after 5 days and 20% in the bile.

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/m2.

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 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 :Act-O-Vial system:
- Solu-Medrol 40 mg Powder and solvent for solution for injection : lactose, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injection
- Solu-Medrol 125 mg – 250 mg Powder and solvent for solution for injection : monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injection

Powder and solvent for solution for injection:
- Solu-Medrol 500 mg – 1000 mg – 2000 mg - Powder and solvent for solution for injection :
  - Powder: monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous.
  - 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 – 2000 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.

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

Unreconstituted product: 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 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 40 mg Powder and solvent for solution for injection: 1 and 3 Act-O-Vials.
Solu-Medrol 125 mg Powder and solvent for solution for injection: 1 Act-O-Vial.
Solu-Medrol 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 1000 mg Powder and solvent for solution for injection: 1 vial + 1 vial.
Solu-Medrol 2000 mg 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.
Solu-Medrol S.A.B. 2000 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

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MANUFACTURED BY

Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, Belgium.

8. PRESCRIPTION STATUS

Prescription only medicine

9. DATE OF REVISION OF THE TEXT

Feb/2018