Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solu-Medrone powder and solvent for solution for injection or concentrate for solution for infusion 125 mg/vial

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Act-o-Vial contains methylprednisolone sodium succinate equivalent to 125 mg of methylprednisolone (62.5 mg/ml following reconstitution).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection or concentrate for solution for infusion.

A white to off-white lyophilised powder, supplied with a clear, colourless solution for reconstitution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Solu-Medrone is indicated for any condition in which rapid and intense corticosteroid effect is required such as:

1. Allergic states, for example:
bronchial asthma, angioneurotic oedema, anaphylaxis.

2. Dermatological conditions
severe erythema multiforme (for example: Stevens-Johnson syndrome).

3. Acute adrenal insufficiency with supplemental salt and/or desoxycorticosterone. Solu-Medrone is not first line treatment for acute adrenal insufficiency because it does not possess sufficient mineralocorticoid properties.

4. Acute systemic lupus erythematosus.

5. Acute rheumatic carditis.

6. Suppression of graft rejection reactions following transplantation.

7. Cerebral oedema secondary to cerebral tumour.

8. The prevention of nausea and vomiting associated with cancer chemotherapy.

9. Ulcerative colitis.

10. Crohn's disease.

11. Aspiration of gastric contents.

12. Acute spinal cord injury. Treatment should begin within eight hours of injury.

13. The treatment of acute exacerbations of multiple sclerosis superimposed on either a relapsing-remitting or chronic progressive background.

4.2 Posology and method of administration

Solu-Medrone may be administered intravenously (injection or infusion) or intramuscularly, the preferred method for emergency use being intravenous injection given over a suitable time interval. When administering Solu-Medrone in high doses intravenously it should be given over a period of at least 30 minutes. Doses up to 250 mg should be given intravenously over a period of at least five minutes.

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).

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

As adjunctive therapy in life-threatening conditions, administer 30 mg/kg IV over a period of at least 30 minutes. The dose may be repeated every 4 to 6 hours for up to 48 hours.

Methylprednisolone IV pulses, consisting of 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: systemic lupus erythematosus. In multiple sclerosis unresponsive to standard therapy (or during exacerbation episodes), administer pulses of 500 or 1000 mg/day for 3 or 5 days over 30 minutes.

As adjunctive therapy in other conditions, the initial dose will vary from 10 to 500 mg IV, depending on the clinical condition. Larger doses may be required for short-term management of severe, acute conditions. Initial doses up to 250 mg should be administered IV over a period of at least 5 minutes, while larger doses should be administered over at least 30 minutes. Subsequent doses may be administered IV or IM at intervals dictated by the patient's response and clinical condition.

For intravenous infusion the initially prepared solution may be diluted with 5% dextrose in water, isotonic saline solution, or 5% dextrose in isotonic saline solution. To avoid compatibility and stability problems with other drugs Solu-Medrone should be administered separately from other drugs whenever possible either as an IV push, through an IV medication chamber, as an IV "piggy-back" solution, or via an infusion pump and only in the diluents mentioned above.

Solu-Medrone 40 mg and 125 mg are each supplied in an Act-o-Vial two compartment vial consisting of adjoining compartments of lyophilised powder and solvent (Sterile Water for Injection).

The following instructions for the use of the Act-o-Vial should be observed: -

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

Parenteral drug products should, wherever possible, be visually inspected for particulate matter and discoloration prior to administration.

Undesirable effects may be minimised by using the lowest effective dose for the minimum period (see section 4.4).

Adults

Dosage should be varied according to the severity of the condition, initial dosage will vary from 10 to 500 mg. In the treatment of graft rejection reactions following transplantation, a dose of up to 1 g/day may be required. Although doses and protocols

have varied in studies using Solu-Medrone in the treatment of graft rejection reactions, the published literature supports the use of doses of this level, with 500 mg to 1 g most commonly used for acute rejection. Treatment at these doses should be limited to a 48 - 72 hour period until the patient's condition has stabilised, as prolonged high dose corticosteroid therapy can cause serious corticosteroid induced side-effects (see section 4.8 and section 4.4).

Elderly patients
Solu-Medrone is primarily used in acute short-term conditions. There is no information to suggest that a change in dosage is warranted in the elderly. Treatment of elderly patients, however, should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age and close clinical supervision is required (see section 4.4).

Paediatric population
In the treatment of high dose indications, such as haematological, rheumatic, renal and dermatological conditions, a dosage of 30 mg/kg/day to a maximum of 1 g/day is recommended. This dosage may be repeated for three pulses either daily or on alternate days. In the treatment of graft rejection reactions following transplantation, a dosage of 10 to 20 mg/kg/day for up to 3 days, to a maximum of 1 g/day, is recommended. In the treatment of status asthmaticus, a dosage of 1 to 4 mg/kg/day for 1 - 3 days is recommended.

The dose may be reduced for infants and children but should be selected based on the severity of the condition and the response of the patient rather than on the average age or weight of the patient. The paediatric dosage should not be less than 0.5 mg/kg every 24 hours.

The following table contains suggested dosing schedules for Solu-Medrone for a range of indications:

Indication	**Dosage**
Rheumatic disorders unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates. 1 g/day for 1 to 4 days, or 1 g/month for six months.
Edematous states, such as glomerulonephritis or lupus nephritis, unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within 1 week after therapy, or as the patient's condition dictates. 30 mg/kg every other day for 4 days, or 1 g/day for 3, 5 or 7 days.
Terminal cancer (to improve quality of life)	Administer 125 mg /day IV for up to 8 weeks.
Pneumocystis jiroveci pneumonia in patients with AIDS	**Therapy should begin within 72 hours of initial anti-pneumocystis treatment.** One possible regimen is to administer 40 mg IV every 6 to 12 hours with gradual tapering over a maximum of 21 days or until the end of pneumocystis therapy. Due to the increased rate of reactivation of tuberculosis in AIDS patients, consideration should be given to the administration of antimycobacterial therapy if corticosteroids are used in this high risk group. The patient should also be observed for activation of other latent infections.
Exacerbation of chronic obstructive pulmonary disease (COPD)	Two dose regimens have been studied: 0.5 mg/kg IV every 6 hours for 72 hours, **or** 125 mg IV every 6 hours for 72 hours, switch to an oral corticosteroid and taper dose. Total treatment period should be at least 2 weeks.

4.3 Contraindications

The usual contraindications to the systemic or local use of corticosteroids should be observed.

Solu-Medrone is contraindicated:

- in patients who have systemic fungal infections and in systemic infection unless specific anti-infective therapy is employed.
- in patients with known hypersensitivity to methylprednisolone or any of the excipients listed in section 6.1.
- for use by the intrathecal route of administration.
- for use by the epidural route of administration.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see section 4.4).

4.4 Special warnings and precautions for use

Immunosuppressant Effects/Increased Susceptibility to Infections
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular or humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunisation with varicella/zoster immunoglobin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.
Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults, particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IVIG) may be indicated. Exposed patients should be advised to seek medical advice without delay.
Administration of live or live, attenuated vaccines is contra-indicated in patients receiving immunosuppressive doses of corticosteroids (see section 4.3). Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.
If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.
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. A systematic review of short-course, high-dose corticosteroids did not support their use. However, meta- analyses, and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor-dependent septic shock.

Immune System Effects

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

Endocrine Effects
In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.
Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy. This effect may be minimized by use of alternate-day therapy.

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

Drug-induced secondary adrenocortical insufficiency may therefore 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.

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

Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease.
There is an enhanced effect of corticosteroids on 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, can increase blood glucose, worsen pre- existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

Psychiatric Effects
Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.
Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

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

Severe medical events have been reported in association with the intrathecal/epidural routes of administration (see section 4.3 and 4.8).

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

Ocular Effects
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. Central serous chorioretinopathy, may lead to retinal detachment.
Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Prolonged use of corticosteroids may produce posterior subcapsular and nuclear cataracts (particularly in children) and, exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Frequent ophthalmic monitoring is necessary.

Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

Cardiac Effects
Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy (see section 4.8).
Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see section 4.8).

There are reports of cardiac arrhythmias, and/or circulatory collapse, and/or cardiac arrest following the rapid administration of large intravenous doses of Solu-Medrone (more than 0.5 g administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, Solu- Medrone, 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.
Steroids should be used with caution in patients with hypertension.

Gastrointestinal Effects
High doses of corticosteroids may produce acute pancreatitis.

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain (see section 4.8). 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.

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary:
Active or latent peptic ulceration.
Fresh intestinal anastomoses.

Abscess or other pyogenic infections.
Ulcerative colitis.
Diverticulitis.

Musculoskeletal Effects
An acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.
Osteoporosis is a common but infrequently recognized adverse effect associated with a long- term use of large doses of glucocorticoid. Post-menopausal females are particularly at risk.

Renal and urinary disorders
Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone.
Corticosteroids should be used with caution in patients with renal insufficiency.

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

Injury, poisoning and procedural complications
Systemic corticosteroids are not indicated for, and therefore should not be used to treat traumatic brain injury as demonstrated by the results of a multicenter study. The study results revealed an increased mortality in the 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

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.

Hepatobiliary Effects
Drug-induced liver injury such as acute hepatitis or liver enzyme increase can result from cyclical pulsed IV 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.

Other
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 as to whether daily or intermittent therapy should be used.
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).

The lowest possible dose of corticosteroid should be used to control the condition under treatment and when reduction in dosage is possible, the reduction should be gradual (see section 4.2).

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see section 4.5).
Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with malignancies, including haematological malignancies and solid tumours, following the use of systemic corticosteroids alone or in combination with

other chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumours that have a high proliferative rate, high tumour burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

Paediatric population
Premature and low-birth weight infants may be more likely to develop toxicity.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and use of such regimen should be restricted to the most urgent indications. Alternate-day glucocorticoid therapy usually minimizes this side effect (see section 4.2).
Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

Hypertrophic cardiomyopathy may develop after administration of methylprednisolone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.
Excipient information:
Solu-Medrone 125 mg contains less than 1 mmol sodium (23 mg) in each vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 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 (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS - Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance 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 - Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result.

CYP3A4 SUBSTRATES - In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration.

NON-CYP3A4-MEDIATED EFFECTS – Other interactions and effects that occur with methylprednisolone are described in Table 1 below.

Table 1 provides a list and descriptions of the most common and/or clinically important drug interactions or effects with methylprednisolone.

Table 1. Important drug or substance interactions/effects with methylprednisolone

Drug Class or Type - DRUG or SUBSTANCE	**Interaction/Effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - RIFAMPICIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when

Drug Class or Type - DRUG or SUBSTANCE	**Interaction/Effect**
	given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (See section 4.4 Musculoskeletal, for additional information.) 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antiemetic - 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 resulting in reduced plasma concentrations.
Pharmacokinetic enhancers - COBICISTAT	CYP3A4 INHIBITORS
Aromatase inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHISTERONE	CYP3A4 INHIBITOR (and SUBSTRATE)
GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Immunosuppressant - 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 drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon coadministration. 2) Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
Macrolide Antibacterial	CYP3A4 INHIBITOR

Drug Class or Type - DRUG or SUBSTANCE	**Interaction/Effect**
- TROLEANDOMYCIN	
NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs (see section 4.8). 2) Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.
Potassium depleting agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists.

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required (see section 4.4).

Incompatibilities
To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate be administered separately from other compounds that are administered via the IV route of administration. Drugs that are physically incompatible in solution with methylprednisolone sodium succinate include, but are not limited to: allopurinol sodium, doxapram hydrochloride, tigecycline, diltiazem hydrochloride, calcium gluconate, vecuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol. (see section 6.2 for additional information.)

4.6 Fertility, pregnancy and lactation

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

Pregnancy
Some corticosteroids readily cross the placenta. There may be a very small risk of cleft palate and intra-uterine growth retardation in the foetus; there is evidence of harmful effects on pregnancy in animals. Neonates of mothers who received such therapy during pregnancy should be observed for signs of hypoadrenalism and appropriate measures instituted if such signs exist. One retrospective study found an increased incidence of low-birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related. Since adequate human reproductive studies have not been done with methylprednisolone sodium succinate, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and foetus. Patients with pre-eclampsia or fluid retention require close monitoring.

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

Breast-feeding
Corticosteroids are excreted in breast milk.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Under normal circumstances Solu-Medrone therapy would be considered as short-term. However, the possibility of side-effects attributable to corticosteroid therapy should be recognised, particularly when high-dose therapy is being used (see section 4.4). Such side-effects include:

Very common ≥1/10, (≥10%)
Common ≥1/100 and <1/10, (≥1% and <10%)
Uncommon ≥1/1000 and <1/100, (≥0.1% and <1%)
Rare ≥1/10,000 and <1/1000, (≥0.01% and <0.1%)
Very rare <1/10,000, (<0.01%)
Not known (cannot be estimated from available data)

System Organ Class	**Frequency†**	**Undesirable Effects**
Infections and infestations	***Not Known***	Opportunistic infection; Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs); Peritonitis[#]; Recurrence of dormant tuberculosis (see section 4.4)
Blood and lymphatic system disorders	***Not Known***	Leukocytosis
Immune system disorders	***Not Known***	Drug hypersensitivity; Anaphylactic reaction; Anaphylactoid reaction
Endocrine disorders	***Not Known***	Cushingoid; Hypothalamic pituitary adrenal axis suppression;Steroid withdrawal syndrome (including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight)
Metabolism and nutrition disorders	***Not Known***	Metabolic acidosis; Sodium retention; Epidural lipomatosis; Fluid retention; Alkalosis hypokalaemic; Dyslipidemia; Glucose tolerance impaired; Increased insulin requirements (or oral hypoglycemic agents in diabetics); Lipomatosis; Increased appetite (which may result in weight increase)
Psychiatric disorders	***Not Known***	Affective disorder (including depressed mood, euphoric mood, affect lability, drug dependence, suicidal ideation); Psychotic disorder (including mania, delusions, hallucinations and schizophrenia); Confusion; Anxiety; Behavioural disturbances; Sleep disturbances; Irritability and cognitive dysfunction including confusion and amnesia have been reported for all corticosteroids. Reactions occur in both adults and children. In adults, the frequency of severe reactions was estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids (the frequency is unknown).

Nervous system disorders	***Not Known***	Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]); Seizure; Amnesia; Cognitive disorder; Dizziness; Headache
Eye disorders	***Not Known***	Chorioretinopathy; Cataract (with possible damage to the optic nerve); Glaucoma; Exophthalmos; Vision blurred (see also section 4.4); Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease
Ear and labyrinth disorders	***Not Known***	Vertigo
Cardiac disorders	***Not Known***	Cardiac failure congestive (in susceptible patients); Arrhythmia
Vascular disorders	***Not Known***	Thrombo-embolism; Thrombotic events Hypertension; Hypotension Flushing
Respiratory, thoracic and mediastinal disorders	***Not Known***	Pulmonary embolism; Hiccups
Gastrointestinal disorders	***Not Known***	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage); Intestinal perforation; Gastric haemorrhage; Pancreatitis; Oesophagitis ulcerative; Oesophagitis; Abdominal distension; Abdominal pain; Diarrhoea; Dyspepsia; Nausea; Oesophageal candidiasis; Vomiting; Bad taste in mouth may occur especially with rapid administration.
Hepatobiliary disorders	***Not Known***	Hepatitis†; Increase of liver enzymes (e.g AST increased, ALT increased)
Skin and subcutaneous tissue disorders	***Not Known***	Angioedema; Hirsutism; Petechiae; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Skin striae; Rash; Pruritus; Urticaria; Acne; Skin hypopigmentation; Telangiectasia
Musculoskeletal and connective tissue disorders	***Not Known***	Muscular weakness; Myalgia; Myopathy; Muscle atrophy; Osteoporosis; Osteonecrosis; Pathological fracture; Neuropathic arthropathy; Arthralgia; Growth retardation
Reproductive system and breast disorders	***Not Known***	Menstruation irregular; Amenorrhoea
General disorders and administration site conditions	***Not Known***	Impaired healing; Oedema peripheral; Fatigue; Malaise; Injection site reaction; Withdrawal symptoms - Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see section 4.4).
Investigations	***Not Known***	Intraocular pressure increased; Carbohydrate tolerance decreased; Blood potassium decreased; Urine calcium increased; Blood alkaline phosphatase increased; Blood urea increased; Suppression of reactions to skin tests*
Injury, poisoning and procedural complications	***Not Known***	Spinal compression fracture; Tendon rupture (particularly of the Achilles tendon)
Neoplasms benign, malignant and unspecified (including cysts and polyps	***Not Known***	Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission; Pheochromocytoma crisis.

* Not a MedDRA PT.

† Hepatitis has been reported with IV administration (see section 4.4).

Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids. Reports of acute toxicity and/or death following overdosage of corticosteroids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic. Following overdosage the possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. Further traumatic episodes during that period may require special supportive therapy. Methylprednisolone is dialysable.

Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB04

Methylprednisolone is a potent corticosteroid with an anti-inflammatory activity at least five times that of hydrocortisone. An enhanced separation of glucocorticoid and mineralocorticoid effect results in a reduced incidence of sodium and water retention.

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:
After a 40 mg IM dose of Solu-Medrone to fourteen healthy adult male volunteers, the average peak concentration of 454 ng/ml was achieved at 1 hour. At 12 hours, the methylprednisolone plasma concentration has declined to 31.9 ng/ml. No methylprednisolone was detected 18 hours after dosing. Based on area-under-the-time-concentration curve, an indication of total drug absorbed, IM Solu-Medrone was found to be equivalent to the same dose administered intravenously.

Results of a study demonstrated that the sodium succinate ester of methylprednisolone is rapidly and extensively converted to the active methylprednisolone moiety after all routes of administration.

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

Distribution:
Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted 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 extensively bound to plasma proteins, mainly to globulin and less so to albumin. Only unbound corticosteroid has pharmacological effects or is metabolised. Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.

Metabolism occurs in the liver and to a lesser extent in the kidney.

In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone.

Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4-mediated metabolism, see Section 4.5). Metabolites are excreted in the urine.

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.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, 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 adrenocortical steroids.

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

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

Reproductive toxicity
Corticosteroids have been shown to reduce fertility when administered to rats. Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids such as methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), and intra-uterine growth retardation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium biphosphate monohydrate
Sodium phosphate
Sodium hydroxide

Solvent:
Sterile Water for Injections

6.2 Incompatibilities

To avoid compatibility problems with other drugs Solu-Medrone should be administered separately, only in the solutions mentioned in section 4.2.

The IV compatibility and stability of Solu-Medrone solutions and with other drugs in intravenous admixtures is 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 sodium Solu-Medrone be administered separately from other drugs and as either IV push, through an IV medication chamber, as an IV "piggy-back" solution, or via an infusion pump.

6.3 Shelf life

2 years.

Reconstituted solution should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.

6.5 Nature and contents of container

Act-o-Vial two compartment vial. The bottom compartment contains the sterile lyophilised powder, separated by a constriction with a rubber centre seal from the upper compartment which holds 2 ml of solvent.

A sterile rubber plunger and activator cap close the aperture of the upper compartment. The solution is formed by mixture of the contents of the two compartments. (See section 4.2).

6.6 Special precautions for disposal and other handling

No diluents other than those referred to in section 4.2 are recommended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/136/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978

Date of latest renewal: 28 January 2006

10 DATE OF REVISION OF THE TEXT

December 2024