Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methylprednisolone 500mg powder and solvent for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains methylprednisolone sodium succinate 663.0 mg equivalent to 500 mg of methylprednisolone. After reconstitution in water for injections, each ml of solution contains the equivalent of 59.6 mg of methylprednisolone.
Each ampoule of solvent contains 7.8 ml of water for injections.
Sodium content: the 500 mg methylprednisolone vials contain the equivalent of 37.4 mg (1.6 mmol) of sodium.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.
Each vial of methylprednisolone sodium succinate contains a white or almost white amorphous powder.
Each ampoule of solvent contains water for injections.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Methylprednisolone powder and solvent for injection/infusion is indicated to treat any condition in which rapid and intense corticosteroid effect is required such as:
1. Dermatological disease
Severe erythema multiforme (Stevens Johnson syndrome)
2. Allergic states
Bronchial asthma
Severe seasonal and perennial allergic rhinitis
Angioneurotic oedema
Anaphylaxis
3. Gastro intestinal diseases
Ulcerative colitis
Crohn's disease
4. Respiratory diseases
Aspiration of gastric contents
Fulminating or disseminated tuberculosis (with appropriate antituberculous chemotherapy)
5. Neurological disorders
Cerebral oedema secondary to cerebral tumour
Acute exacerbations of multiple sclerosis superimposed on a relapsing/remitting background.
6. Miscellaneous
T.B. meningitis (with appropriate antituberculous chemotherapy)
Transplantation

4.2 Posology and method of administration

Posology

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

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 problems with other drugs Methylprednisolone powder for injection/infusion should be administered separately, only in the solutions mentioned.

Undesirable effects may be minimised by using the lowest effective dose for the minimum period (see Other special warnings and precautions).

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

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 gram/day may be required. Although doses and protocols have varied in studies using methylprednisolone sodium succinate 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 Undesirable effects and Special warnings and special precautions for use).

Children: In the treatment of high dose indications, such as haematological, rheumatic, renal and dermatological conditions, a dosage of 30mg/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 20mg/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 4mg/kg/day for 1- 3 days is recommended.

Elderly patients: Methylprednisolone sodium succinate powder for injection/infusion is primarily used in acute short term conditions. There is no information to suggest that a change in dosage is warranted in the elderly. However, treatment of elderly patients 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 Special warnings and special precautions for use).

Detailed recommendations for adult dosage are as follows:

In anaphylactic reactions adrenaline or noradrenaline should be administered first for an immediate haemodynamic effect, followed by intravenous injection of methylprednisolone sodium succinate with other accepted procedures. There is evidence that corticosteroids through their prolonged haemodynamic effect are of value in preventing recurrent attacks of acute anaphylactic reactions.

In sensitivity reactions Methylprednisolone sodium succinate is capable of providing relief within one half to two hours. In patients with status asthmaticus Methylprednisolone sodium succinate may be given at a dose of 40 mg intravenously, repeated as dictated by patient response. In some asthmatic patients it may be advantageous to administer by slow intravenous drip over a period of hours.

In graft rejection reactions following transplantation doses of up to 1 g per day have been used to suppress rejection crises, with doses of 500 mg to 1 g most commonly used for acute rejection. Treatment should be continued only until the patient's condition has stabilised; usually not beyond 48 - 72 hours.

In cerebral oedema corticosteroids are used to reduce or prevent the cerebral oedema associated with brain tumours (primary or metastatic).

In patients with oedema due to tumour, tapering the dose of corticosteroid appears to be important in order to avoid a rebound increase in intracranial pressure. If brain swelling does occur as the dose is reduced (intracranial bleeding having been ruled out), restart larger and more frequent doses parenterally. Patients with certain malignancies may need to remain on oral corticosteroid therapy for months or even life. Similar or higher doses may be helpful to control oedema during radiation therapy.

The following are suggested dosage schedules for oedemas due to brain tumour.

Schedule A (1)	**Dose (mg)**	**Route**	**Interval in hours**	**Duration**
Pre-operative:	20	IM	3-6	
During Surgery:	20 to 40	IV	Hourly	
Post operative:	20	IM	3	24 hours

	16	IM	3	24 hours
	12	IM	3	24 hours
	8	IM	3	24 hours
	4	IM	3	24 hours
	4	IM	6	24 hours
	4	IM	12	24 hours

Schedule B (2)	Dose (mg)	Route	Interval in hours	Duration
Pre-operative:	40	IM	6	2-3
Post operative:	40	IM	6	3-5
	20	Oral	6	1
	12	Oral	6	1
	8	Oral	8	1
	4	Oral	12	1
	4	Oral		1

Aim to discontinue therapy after a total of 10 days.

In the treatment of acute exacerbations of multiple sclerosis in adults, the recommended dose is 1000 mg daily for 3 days. Methylprednisolone powder for injection/infusion should be given as an intravenous infusion over at least 30 minutes.

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. The initial dose, up to 250 mg, should be given intravenously over a period of at least 5 minutes, doses exceeding 250 mg should be given intravenously over a period of 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.

Method of administration

To be administered intravenously or intramuscularly.

4.3 Contraindications

Methylprednisolone powder for injection/infusion is contraindicated:

- in patients who have systemic fungal infections unless specific anti-infective therapy is employed and in cerebral oedema in malaria.
- in patients with known hypersensitivity to methylprednisolone or any component of the formulation.
- for use by the intrathecal route of administration.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

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. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentations may often be atypical and may reach an advanced stage before being recognised.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

Chickenpox is of serious concern since this normally minor illness may be fatal in the 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 immunization 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.

Exposure to measles should be avoided. Medical advice should be sought immediately if exposure occurs. Prophylaxis with normal intramuscular immuneglobulin may be needed.

Similarly, corticosteroids should be used with great care in patients with known or suspected parasitic infections such as Strongyloides (threadworm) infestation, which may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicaemia. Although Methylprednisolone is not approved for use in any shock indication, the following warning statement should be adhered to. Data from clinical study conducted to establish the efficacy of methylprednisolone 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. Therefore this product should not be used in the treatment of septic syndromes or septic shock.

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.

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

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 anti-tuberculosis 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.

Blood and Lymphatic System

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids.

Immune System Effects

Allergic reactions may occur. Rarely skin reactions and anaphylactic/anaphylactoid reactions have been reported following parenteral methylprednisolone therapy. Physicians using the drug should be prepared to deal with such a possibility. Appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of drug allergy.

Endocrine Effects

Pharmacological 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 an alternate-day therapy.

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

Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. In patients who have received more than physiological doses of systemic corticosteroids (approximately 6 mg methylprednisolone) for greater than 3 weeks, withdrawal should not be abrupt.

Drug-induced secondary adrenocortical insufficiency may therefore be minimised by the gradual reduction of dosage. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids, but there is uncertainty about HPA suppression, the dose of systemic corticosteroids may be reduced rapidly to physiological doses. Once a daily dose of 6 mg methylprednisolone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 32 mg daily of methylprednisolone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 32 mg daily of methylprednisolone.
- Patients repeatedly taking doses in the evening.

Patients should carry ‘Steroid Treatment’ cards which can give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and duration of treatment.

This type of relative insufficiency may persist for months after discontinuation of therapy, therefore, in any situations of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or mineralocorticoid should be administered concurrently.

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroid before, during and after stress situation is indicated.

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 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. Frequent patient monitoring is necessary in patients with hypothyroidism.

Metabolism and Nutrition

Frequent patient monitoring is necessary in patients with diabetes mellitus (or a family history of diabetes). Corticosteroids including methylprednisolone can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

Psychiatric Effects

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 Interactions with other medicinal products and other forms of interaction that can increase the risk of side effects), 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.

Frequent patient monitoring is necessary in patients with existing or previous history of severe affective disorders (especially previous steroid psychosis).

Nervous System Effects

Corticosteroids should be used with caution in patients with seizure disorders. Frequent patient monitoring is necessary in patients with epilepsy.

Corticosteroids should be used with caution in patients with myasthenia gravis (also see myopathy statement in Musculoskeletal Effects section below). Frequent patient monitoring is necessary in patients with myasthenia gravis).

Ocular Effects

Frequent patient monitoring is necessary in patients with glaucoma (or a family history of glaucoma) and in patients with ocular herpes simplex, for fear of corneal perforation.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. 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 alternated day therapy may reduce the incidence of complications in corticosteroid therapy.

There have been a few reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest associated with the rapid intravenous administration of large doses of methylprednisolone (greater than 500 mg 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 and duration of infusion.

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

Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see section 4.8).

Frequent patient monitoring is necessary in patients with congestive heart failure or recent myocardial infarction (myocardial rupture has been reported).

Vascular Effects

Steroids should be used with caution in patients with hypertension. Frequent patient monitoring is necessary.

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.

Gastrointestinal Effects

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.

Particular pain is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary:

Ulcerative colitis

Perforation, Abscess or other pyogenic infections

Diverticulitis

Fresh intestinal anastomoses

Peptic ulceration

Hepatobiliary Effects

High doses of corticosteroids may produce acute pancreatitis

Drug induced liver injury including 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.

Musculoskeletal Effects

Particular care is required when considering the use of systemic corticosteroids in patients with myasthenia gravis or osteoporosis (post-menopausal females are particularly at risk) and frequent patient monitoring is necessary.

Osteoporosis is a common but infrequently recognised adverse effect associated with long-term use of large doses of glucocorticoid.

Renal and Urinary Disorders

Particular care is required when considering the use of systemic corticosteroids in patients with renal insufficiency and frequent patient monitoring is necessary.

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 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

Corticosteroids should not be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

Other Adverse Events

Since complications of treatment with glucocorticoids are dependent on the size of the dose and 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.

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.

Paediatric population

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 avoids or minimizes this side effect.

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

Elderly

The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Caution is recommended with prolonged corticosteroid treatment in the elderly due to a potential increase risk for osteoporosis, as well as increased risk of fluid retention with possible resultant hypertension. Close clinical supervision is required to avoid life-threatening reactions.

Sodium content: each 1000 mg of methylprednisolone contains the equivalent of 3.2 mmol (74.4 mg) of sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Methylprednisolone is a cytochcrome P450 enzyme (CYP) substrate and is mainly metabolised by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6β-compounds of steroids, the essential Phase 1 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 glucococorticoid 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 s 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 substrate for CYP3A4. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result.

CYP3A4 SUBSTRATE – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be inhibited or induced, 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 2 below.

Table 2 provides a list and description of the most common and/or clinically important drug interactions or effects with methylprednisolone.

Table 2. Important drug or substrate interactions/effects with methylprednisolone

Drug Class or Type **- DRUG or SUBSTANCE**	**Interaction**	**Effect**
Macrolide Antibacterial - TROLAENDOMYCIN Antibacterial - ISONIAZID - GRAPEFRUIT JUICE	CYP3A4 INHIBITOR	CYP3A4 INHIBITOR An increase in the plasma concentration of methylprednisolone may occur. The dose of methylprednisolone may need to be treated to avoid steroid toxicity. In addition, there is a potential effect of methylprednisolone on the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - RIFAMPIN Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCER	CYP3A4 INDUCER A decrease in the plasma concentration of methylprednisolone may occur. Co-administration may require an increase in methylprednisolone dosage to achieve the desired result.
Antiemetic -APREPITANT - FOSAPREPITANT Antifungal - ITRACONAZOLE - KETOCONAZOLE Antivirals -HIV-PROTEASE	CYP3A4 INHIBITORS (and SUBSTRATES)	CYP3A4 INHIBITORS (and SUBSTRATES) The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the

INHIBITORS Calcium Channel Blocker -DILTIAZEM Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHISTERONE Immunosuppressant -CICLOSPORIN Macrolide Antibacterial -CLARITHROMYCIN -ERYTHROMYCIN		use of either drug alone may be more likely to occur with administration. **Protease inhibitors**, such as indinavir and ritonavir, may increase plasma concentration of corticosteroids. **Ciclosporin** 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.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATES)	CYP3A4 INDUCER (and SUBSTRATES) The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with administration.
Immunosuppressant -CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES	CYP3A4 SUBSTRATES The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with administration.
Anticoagulants (oral)	Non-CYP3A4-mediated effects	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticholinergics		Corticosteroids may influence the

-NEUROMUSCULAR BLOCKERS		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 Warnings and Precautions, 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.
Antidiabetics		Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required
Aromatase inhibitors -AMINOGLUTETHIMIDE		Aminoglutethimide-induced adrenal suppression may impede endocrine changes caused by prolonged glucocorticoid treatment.
NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)		1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Methylprednisolone may increase the clearance of high-dose aspirin. This decrease in salicylate serum levels could lead to an increased risk of salicylate toxicity when methylprednisolone is withdrawn.
Potassium depleting agents -DIURETICS -AMPHOTEICIN B -BETA$_2$ AGONISTS -XANTHENES		When corticosteroids are administered concomitantly with potassium depleting agents patients should be observed closely for development of hypokalemia. Corticosteroids antagonise the diuretic effect of diuretics.

Corticosteroids antagonise the hypotensive effect of all antihypertensives.

There is an increased risk of hypokalaemia when corticosteroids are given with cardiac glycosides.

The effects of corticosteroids may be reduced for 3-4 days after mifepristone.

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

There is no evidence that corticosteroids impair fertility. In women treatment with corticosteroids can lead to menstrual irregularities.

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs, however, methylprednisolone does cross the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate in man, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

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

Breast-feeding

Corticosteroids are excreted in small amounts in breast milk, however, doses of up to 40 mg daily of methylprednisolone are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression, but the benefits of breastfeeding are likely to outweigh any theoretical risk.

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 Methylprednisolone powder for injection/infusion 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:

MedDRA System Organ Class	**Frequency***	**Undesirable Effects**
Infections and infestations	Common	Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs)
	Not known	Opportunistic infection Recurrence of dormant tuberculosis (see section 4.4)
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
Blood and lymphatic system disorders	Not known	Leucocytosis

Immune system disorders	Not known	Drug hypersensitivity (including anaphylactic reaction and anaphylactoid reaction with or without circulatory collapse, cardiac arrest, bronchospasm
Endocrine disorders	Common	Cushingoid
	Not known	Hypopituitarism (including suppression of the hypothalamo-pituitary-adrenal axis), steroid withdrawal syndrome (including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight)
Metabolism and nutrition disorders	Common	Sodium retention; fluid retention
	Not known	Glucose tolerance impaired; alkalosis hypokalaemic; dyslipidemia; increased requirements for insulin (or oral hypoglycaemic agents in diabetics; negative nitrogen balance (due to protein catabolism); blood urea increased; increased appetite (which may result in weight increased), lipomatosis, epidural lipomatosis.
Psychiatric disorders	Common	A wide range of psychiatric reactions include affective disorders (such as irritable, euphoric, depressed and labile moods psychological dependence and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances , irritability, anxiety, sleep disturbances, cognitive dysfunction including confusion and amnesia have been reported for all corticosteroids. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions was estimated to be a 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown
Nervous system disorders	Not known	Increased intracranial pressure with papilloedema [benign intracranial hypertension]; convulsion, amnesia, cognitive disorder; dizziness; headache
Eye disorders	Common	Posterior subcapsular cataracts
	Not known	Exophthalmos; glaucoma; papilloedema with possible damage to the optic nerve, corneal or scleral thinning; chorioretinopathy; exacerbation of ophthalmic viral or fungal disease
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Congestive heart failure in susceptible patients, arrhythmia
Vascular disorders	Common	Hypertension

	Not known	Hypotension; thromboembolism; thrombotic events
Respiratory, thoracic and mediastinal disorders	Not known	Hiccups
Gastrointestinal disorders	Common	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage)
	Not known	Gastric haemorrhage; intestinal perforation; pancreatitis; peritonitis; ulcerative oesophagitis; oesophagitis; oesophageal candidiasis; abdominal pain; abdominal distension; diarrhoea; dyspepsia; nausea; vomiting; bad taste in mouth may occur especially with rapid administration
Hepatobiliary Effects	Not known	Hepatitis; Increase of liver enzymes
Skin and subcutaneous tissue disorders	Common	Peripheral oedema; ecchymosis; skin atrophy (thin fragile skin); acne
	Not known	Angioedema; petechiae; skin striae; telangiectasia; skin hypopigmentation or hyperpigmentation; hirsutism; rash; erythema; pruritus; urticaria; hyperhidrosis
Musculoskeletal and connective tissue disorders	Common	Growth retardation (in children); osteoporosis; muscular weakness
	Not known	Osteonecrosis; pathological fracture; muscle atrophy; myopathy; neuropathic arthropathy; arthralgia; myalgia
Reproductive system and breast disorder	Not known	Irregular menstruation, amenorrhoea
General disorders and administration site conditions	Common	Impaired wound healing
	Not known	Injection site reaction; fatigue; malaise; 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	Common	Blood potassium decreased (potassium loss)
	Not known	Alanine aminotransferase increased (ALT, SGPT); aspartate aminotransferase increased (AST, SGOT); these changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation. Blood alkaline phosphotase increased; intraocular pressure increased; carbohydrate tolerance decreased; urine calcium increased; suppression of reactions to skin tests

Injury, poisoning and procedural complications	Not known	Tendon rupture (particularly of the Achilles tendon); spinal compression fracture (vertebral compression fractures)

*Common (>1/100 to <1/10); Uncommon (>1/1,000 to <1/100); Rare (>1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data)

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, Earlsfort Terrace, IRL- Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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. Methylprednisolone is dialysable. Following chronic overdosage the possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. In such event the patient may require to be supported during any further stressful episode.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB04

Methylprednisolone is a 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.

5.2 Pharmacokinetic properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Distribution
Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk.

The plasma protein binding of methylprednisolone in humans is approximately 77%.

Metabolism
Methylprednisolone is extensively bound to plasma proteins, mainly to globulin and less to albumin. Only bound corticosteroid has pharmacological effects or is metabolised. Metabolism occurs in the liver and to a lesser extent in the kidney. In humans, methylprednisolone is metabolised in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone.

Metabolism in the liver occurs primarily via CYP3A2 (for a list of drug interactions based on CYP3A4-mediated metabolism, see section 4.5).

Elimination
Metabolites are excreted in the urine.

The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Its apparent volume of distribution is approximately 1.4 mL/kg and its total clearance is approximately 5 to 6 mL/min/kg. Mean elimination half-life ranges from 2.4 to 3.5 hours in normal healthy adults and appears to be independent of the route of administration.

Total body clearance following intravenous or intramuscular injection of methylprednisolone to healthy adult volunteers is approximately 15-16l/hour. Peak methylprednisolone plasma levels of 33.67 mcg/100 ml were achieved in 2 hours after a single 40 mg i.m. injection to 22 adult male volunteers. Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.

No dosing adjustments are necessary in renal failure. Methylprednisolone is haemodialysable.

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 were those expected to occur with continued exposure to exogenous adrenocortical steroids.

There was no evidence of a potential for genetic and chromosome mutations in limited studies performed in bacteria and mammalian cells. Long-term studies in animals have not been performed to evaluate carcinogenic potential, as the drug is indicated for short-term treatment only.

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 induce malformations (cleft palate, skeletal malformations) and intra-uterine growth retardation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate dibasic.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf-life of the medicinal product as packaged for sale: 2 years.

After reconstitution with Sterile Water for Injections, use immediately, discard any remainder.

6.4 Special precautions for storage

This product does not require any special temperature storage conditions.

Keep the vials/ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Powder

Type I clear glass vial with butyl rubber plug and flip top seal.

Each vial contains the equivalent of 500 mg of methylprednisolone as the sodium succinate for reconstitution with 7.8 ml of Water for Injections.

Solvent

Type I clear glass ampoule.

Each ampoule contains 7.8 ml of Water for Injections.

6.6 Special precautions for disposal

After reconstitution, the solution should be clear and colourless. Parenteral drug products should wherever possible be visually inspected for particulate matter and discoloration prior to administration.

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 problems with other drugs, the reconstituted methylprednisolone solution should be administered separately, only in the solutions mentioned.

7 MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Limited
DCC Vital Westminster Industrial Estate
Repton Road
Measham
DE12 7DT
England

8 MARKETING AUTHORISATION NUMBER

PA1312/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th July 2011

10 DATE OF REVISION OF THE TEXT

June 2017