SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methylprednisolone 40 mg Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Methylprednisolone 40 mg contains 53.0 mg of methylprednisolone sodium succinate, equivalent to 40 mg of methylprednisolone.

Excipient with known effect: This presentation contains less than 1 mmol sodium (23mg) per 40mg, i.e. essentially “sodium-free”.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

Each vial of methylprednisolone sodium succinate contains a white or nearly white amorphous powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methylprednisolone sodium succinate is indicated to treat the following conditions:

1. Endocrine diseases

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone are the medicines of choice, however, synthetic analogues can be used in combination with mineralocorticoids; in children, it is of particular importance to supplementary administration of mineralocorticoids).

Acute adrenocortical insufficiency (hydrocortisone or cortisone are the medicines of choice; conjugation with mineralocorticoids may be necessary, particularly when using its synthetic analogues).

Pre-operatively and in case of trauma or serious illness, in patients with adrenocortical insufficiency or when the adrenal reserve is doubtful:

- Congenital adrenal hyperplasia;
- Non-suppurative thyroiditis;
- Hypercalcemia associated with cancer.

2. Rheumatic diseases

Methylprednisolone is used as an adjuvant therapy for short-term administration to relieve the patient in the event of an acute episode or exacerbation of:

- Post-traumatic osteoarthritis;
- Osteoarthritis synovitis;
- Rheumatoid arthritis including juvenile idiopathic arthritis (certain cases may require low dose maintenance therapy);
- Acute and subacute bursitis;
- Epicondylitis;
- Acute non-specific tenosynovitis;
- Acute gouty arthritis;
- Psoriatic arthritis;
- Ankylosing spondylitis.

3. Collagen and immunocomplex diseases

During an exacerbation or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus (and lupus nephritis);
- Acute rheumatic carditis;
- Systemic dermatomyositis (polymyositis);
- Polyarthritis nodosa;
- Goodpasture's syndrome.

4. Dermatological diseases

- Pemphigus;
- Severe multiforme erythema (Stevens-Johnson syndrome);
- Exfoliative dermatitis;
- Severe psoriasis;
- Bullous herpetiform dermatitis;
- Severe seborrheic dermatitis;
- Mycosis fungoides.

5. Allergic conditions

Control of severe or debilitating allergic situations that cannot be treated with conventional therapy:

- Bronchial asthma;
- Contact dermatitis;
- Atopic dermatitis;
- Serum sickness;
- Hypersensitivity reactions to medicines;
- Post-transfusion urticarial reactions;
- Non-infectious acute laryngeal oedema (epinephrine is the first-line drug).

6. Ophthalmic diseases

Methylprednisolone is indicated for severe acute and chronic allergic and inflammatory processes of the eyes, such as ophthalmic herpes zoster, iritis, iridocyclitis, chorioretinitis, choroiditis and diffuse posterior uveitis, optic neuritis, sympathetic ophthalmia, inflammation of the anterior segment, allergic conjunctivitis, allergic marginal corneal ulcers and keratitis.

7. Gastrointestinal diseases

To manage critical periods of illness in:

- Ulcerative colitis;
- Regional enteritis.

8. Respiratory diseases

Methylprednisolone is indicated in cases of:
- Symptomatic sarcoidosis;
- Beriliosis;
- Fulminant or disseminated pulmonary tuberculosis (when used concomitantly with appropriate antituberculosis chemotherapy);
- Loeffler's syndrome (not treatable by other means);
- Aspiration pneumonitis.

Pneumocystis jiroveci pneumonia

Methylprednisolone is beneficial as an adjuvant in the treatment of patients with acquired immunodeficiency syndrome (AIDS) with moderate to severe pneumonia caused by *Pneumocystis jiroveci* as long as it is administered during the first 72 hours following the institution of antipneumocystosis treatment.

9. Haematological diseases

Acquired haemolytic anaemia (autoimmune), idiopathic thrombocytopenic purpura in adults (intravenous administration only; the intramuscular route is contraindicated), secondary thrombocytopenia in adults, erythroblastopenia (red blood cell anaemia), congenital hypoplastic anaemia (erythroid).

10. Neoplastic diseases

For the palliative treatment of leukaemia and lymphomas in adults and acute childhood leukaemia.
- Hypercalcaemia associated with cancer;
- Terminal cancer: to improve the quality of life of patients with terminal cancer:
- Prevention of nausea and vomiting associated with neoplastic chemotherapy.

11. Oedematous states

For induction of diuresis or remission of proteinuria in nephrotic syndrome, without uraemia, idiopathic or due to erythematosus lupus.

12. Nervous system
- Cerebral oedema due to brain tumour - primary or metastatic and/or associated with surgery or radiotherapy;
- Acute exacerbation of multiple sclerosis;
- Acute vertebro-medullary injuries. Treatment should begin within 8 hours of the injury.

13. Cardiovascular disorders

Shock secondary to adrenocortical insufficiency or conventional therapy-resistant shock when there is possible involvement of corticoadrenal insufficiency (hydrocortisone is generally the drug of choice. When mineralocorticoid activity is undesirable, methylprednisolone is preferred).

14. Haemorrhagic, traumatic and surgical shock

Although no controlled clinical trials have been carried out (double blind, controlled with placebo), results from animal studies indicate that methylprednisolone may be useful in states of haemorrhagic, traumatic and surgical shock resistant to conventional therapy (e.g. fluid replacement, etc.).
See "Special warnings and precautions for use" with reference to septic shock.

15. Other indications

- Tuberculous meningitis with subarachnoid block or threatened block, when used concomitantly with antituberculosis chemotherapy.
- Trichinosis with neurological or myocardial involvement.
- Organ transplantation.
- Prevention of nausea and vomiting associated with neoplastic chemotherapy.

4.2 Posology and method of administration

Methylprednisolone may be administered by intravenous (IV) or intramuscular (IM) injection or by intravenous infusion. The preferred method for initial emergency treatment is intravenous injection.

Dose adjustments are variable and must be individualized, taking into account the disease to be treated, its severity and the patient's response throughout the duration of the treatment. A risk/benefit decision must be made in each individual case and continuously.

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

If, after long-term therapy, the medication is to be stopped, it is necessary to be withdrawn gradually rather than abruptly (see section 4.4).

After the initial emergency period, consideration should be given to using a longer acting injectable preparation or an oral formulation.

As a therapeutic adjuvant in life-threatening situations, administer 30 mg/kg of succinate methylprednisolone sodium IV over a minimum period of 30 minutes. This dose can be repeated every 4 to 6 hours, up to 48 hours.

Intermittent IV administration of 250 mg/day or more for a few days (usually ≤ 5 days), may be appropriate in exacerbation phases and situations that do not respond to conventional therapy, such as: rheumatic diseases; systemic lupus erythematosus; oedematous states, such as glomerulonephritis or lupus nephritis. In multiple sclerosis, in situations that do not respond to conventional therapy (or in exacerbation phases), intermittent administration of 500 mg/day or 1000 mg/day, for 3 days or 5 days, during at least 30 minutes.

In adjuvant therapy for other pathologies, the initial dose varies from 10 to 500 mg IV, depending on the clinical situation being treated. Higher doses may be necessary for short-term treatment of serious acute situations. Initial doses up to 250 mg should be administered by IV route over a minimum period of 5 minutes and higher doses should be administered for at least 30 minutes. Subsequent doses should be administered by IV or IM route, at intervals dictated by the patients' response and their clinical situation.

To administer the medicine intravenously or intramuscularly, the solution should be prepared according to the instructions (see section 6).

In order to avoid compatibility and stability problems, it is recommended that methylprednisolone succinate is administered separately from other substances administered intravenously (see sections 4.5 and 6.6).

Paediatric population
The dosage can be reduced for infants and children but should be defined more by the severity of the situation and response to therapy than by the patient's age or weight. Should not be less than 0.5 mg/kg every 24 hours.

Renal insufficiency
No dose adjustments are necessary in renal failure. Methylprednisolone is haemodialysable.

Liver failure
No dose adjustments are necessary in hepatic failure.

4.3 Contraindications

Methylprednisolone sodium succinate is contraindicated:

- in patients with systemic fungal infections.
- in patients with hypersensitivity to the active substance or any of the excipients mentioned in section 6.1.
- for intrathecal administration.
- for use by the epidural route of administration.

The 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 effect/Increased susceptibility to infections

Corticosteroids may increase susceptibility to infections, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids are used. Pathogenic infections, including viral, bacterial, fungal, protozoan or by 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 become severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Individuals taking medications which suppress the immune system are more susceptible to infections than healthy individuals. For example, chickenpox and measles can have a more serious, or even fatal, course in non-immune children or adults on corticosteroids.

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

may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines can be decreased. Indicated immunisation 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 in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

The role of corticosteroids in septic shock has been controversial, with initial studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients in established septic shock patients 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 administrations (5-11 days) of low doses of corticosteroids can reduce mortality.

Effects on the immune system

Allergic reactions may occur. Due to the fact that, although rarely, cutaneous and anaphylactic/anaphylactoid reactions occur in patients receiving corticosteroid therapy, it is convenient to institute preventive measures before administration, especially in patients with history of allergy to any other drug.

Endocrine effects

In patients on corticosteroid therapy subject to unusual stress, increased dosage of fast-acting corticosteroids before, during and after the stressful situation is indicated. Pharmacological doses of corticosteroids administered over prolonged periods of time can result in hypothalamic-pituitary-adrenal suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced are variable between patients and depends on dose, frequency, time of administration and duration of glucocorticoid therapy. This effect can be minimized by use of alternate-day therapy.

Additionally, fatal acute adrenal insufficiency may occur if glucocorticoids are removed abruptly.

Drug-induced adrenocortical insufficiency can be minimized by gradually reducing the dose. This type of relative insufficiency can persist for months after therapy withdrawal; therefore, in any stressful situation that occurs during this period, hormone therapy must be reinstituted.

A steroid “withdrawal syndrome” may also occur, apparently not related to adrenal insufficiency, after abrupt interruption of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, peeling, myalgia, weight loss and/or hypotension. These effects are thought to be due

to a sudden change in glucocorticoid concentration and not due to low corticosteroids levels.

Glucocorticoids should be avoided in patients with Cushing's disease as they may cause or worsen Cushing's syndrome.
A potentiation of the effect of corticosteroids is observed in patients with hypothyroidism.

Metabolism and Nutrition

Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes, and predispose individuals on long-term corticosteroid therapy to diabetes mellitus.

Psychiatric effects

During treatment with corticosteroids, psychiatric changes may occur, ranging from euphoria, insomnia, mood changes, personality changes and severe depression to clearly psychotic manifestations. If there is emotional instability or psychotic tendencies, they can worsen with the use of corticosteroids.

Potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms generally appear within a few days or weeks of starting treatment. Most reactions disappear after dose reduction or withdrawal, although specific treatment may be required. Psychological effects have been reported after withdrawal of corticosteroids, but its frequency is unknown. Patients/caregivers should be alerted to seek medical assistance if patients develop psychological symptoms, particularly if depressed mood or suicidal ideation are suspected. Patients/caregivers should be alerted to possible psychiatric disorders that may occur during, or immediately after, dose reduction/withdrawal of systemic steroids.

Effects on the Nervous System

Corticosteroids should be used with caution in patients with seizure disorders.

Corticosteroids should be used with caution in patients with myasthenia gravis (see also information on myopathy in the "Musculoskeletal effects" section below).

Although controlled clinical trials have shown that corticosteroids are effective in quickly resolving acute exacerbations of multiple sclerosis, they do not prove that corticosteroids affect the final outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see 4.2 Posology and method of administration).

Serious events associated with intrathecal/epidural routes of administration have been reported (see section 4.8).

Cases of epidural lipomatosis have been reported in patients using corticosteroids, generally in cases of prolonged use at high doses.

- 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.

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.

Prolonged use of corticosteroids can cause posterior subcapsular cataracts and nuclear cataracts (especially in children), exophthalmos, or increased intraocular pressure, which can result in glaucoma with possible damage to the optic nerves. There can be an increase in secondary eye infections due to fungi or viruses in patients receiving glucocorticoids.

Corticosteroids should be used with caution in patients with ocular herpes simplex due to possible corneal perforation.

Corticosteroid therapy has been associated with central serous chorioretinopathy, which can cause retinal detachment.

Cardiac effects

The adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidaemia and hypertension, may predispose patients treated with cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Likewise, corticosteroids must be used judiciously in such patients and particular attention must be given to risk modification and additional cardiac monitoring, if needed. Low doses and alternate-day therapy may reduce the incidence of complications of corticosteroid therapy.

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

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

Vascular effects

Cases of thrombosis including venous thromboembolism have been reported with the use of corticosteroids. Therefore, corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

Corticosteroids should be used with caution in patients with hypertension.

Gastrointestinal effects

High doses of corticosteroids can cause acute pancreatitis.
There is no widespread consensus on whether corticosteroids "per se" are responsible for peptic ulcers detected during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcers, so that perforation or bleeding may occur without significant pain. Glucocorticoid therapy can mask peritonitis or other signs and symptoms associated with gastrointestinal problems, such as perforation, obstruction and pancreatitis. The risk of developing gastrointestinal ulcers increases when corticosteroids are combined with non-steroidal anti-inflammatories steroids (NSAIDs).

Corticosteroids should be used with caution in nonspecific ulcerative colitis if there is a likelihood of perforation, abscess or other pyogenic infection, diverticulitis, recent intestinal anastomoses, active or latent peptic ulcer.

Hepatobiliary effects

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.
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.

Musculoskeletal effects

Acute myopathy has been reported with the use of high doses of corticosteroids, more common in patients with neuromuscular transmission disorders (e.g. myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking agents (e.g. pancuronium). This acute myopathy is generalized, may involve respiratory and ocular muscles, and may result in quadriparesis. An increase in creatine kinase can occur. Clinical improvement or recovery after stopping corticosteroids may take weeks to years.
Osteoporosis is a common but infrequently identified side effect in association with long-term therapy with high doses of glucocorticoids.

Kidney and urinary disorders

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

Corticosteroids should be used with caution in patients with renal insufficiency.

Complementary diagnostic tests

Medium and high doses of hydrocortisone or cortisone can cause an increase in blood pressure, salt and water retention and increased potassium excretion. 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.

Complications of interventions related to injuries and poisoning

The use of systemic corticosteroids is not recommended and should therefore not be used to treat traumatic brain injuries. A multicentre study revealed an increased mortality at week 2 and 6 months after injury, in patients administered methylprednisolone sodium succinate compared to placebo. It was not established a causal relationship with the methylprednisolone sodium succinate.

Other warnings and precautions

Since reactions associated with glucocorticoids are dependent on the dose and duration of the treatment, the possible risks/benefits must be considered in each case individually, both in terms of dose and duration of treatment. Suitability of daily or intermittent therapy should also be considered.

The lowest possible dose of corticosteroids should be administered to control the disease being treated and, if dose reduction is possible, this should be done in gradually.

In post-marketing experience, tumour lysis syndrome (TLS) has been reported in patients with malignant neoplasms, including haematological neoplasms and solid tumours, after the use of systemic corticosteroids alone or in combination with others chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumours with a high proliferative rate, high tumour burden and high sensitivity to cytotoxic agents, must be closely monitored and appropriate precautions must be taken.

Acetylsalicylic acid and non-steroidal anti-inflammatory drugs should be used with caution when administered in combination with corticosteroids.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or confirmation of pheochromocytoma after appropriate risk/benefit assessment.

It is expected that treatment in combination with CYP3A inhibitors, including medicinal products that contain cobicistat, increase the risk of systemic side effects. This combination must be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored regarding these effects.

Paediatric population

The growth and development of infants and children in prolonged corticosteroid therapy should be carefully monitored. Growth suppression may occur in children on long-term daily therapy with divided doses of glucocorticoids. The use of this therapy should be reserved for urgent situations only. An alternate day therapeutic regimen usually avoids or minimizes this side effect.

Infants and children receiving long-term corticosteroid therapy are at special risk of an increase in intracranial pressure.

High doses of corticosteroids can produce pancreatitis in children.

Hypertrophic cardiomyopathy may develop following administration of methylprednisolone to premature babies and, therefore, an appropriate diagnostic assessment and monitoring of cardiac function and structure should be carried out

Excipient information

Sodium
Methylprednisolone 40 mg contains less than 1 mmol sodium (23 mg) per 40 mg, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Methylprednisolone is an enzyme substrate of cytochrome P450 (CYP) and is mainly metabolized by the CYP3A4 enzyme. The CYP3A4 enzyme is the dominant enzyme in CYP subfamily most common in the liver of adult humans. This enzyme catalyses 6β-hydroxylation of steroids, the essential phase I metabolic step for endogenous and synthetic corticosteroids. Many other compounds are also CYP3A4 substrates, some of which (as well as other drugs) have been shown to modify glucocorticoids metabolism by induction (positive regulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 inhibitors – drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase plasma concentrations of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, methylprednisolone dose may need to be adjusted to avoid toxicity by this steroid.

CYP3A4 inducers - medications that induce CYP3A4 activity generally increase hepatic clearance, resulting in a decreased plasma concentration of medicines that are CYP3A4 substrates. Simultaneous administration may require an increase of the dose of methylprednisolone to achieve the desired result.

CYP3A4 substrates - in the presence of another CYP3A4 substrate, methylprednisolone hepatic clearance may be affected, requiring corresponding dose adjustments. It is possible that adverse events associated with the use of each drug alone may be more likely to occur in the case of simultaneous administration.

Effects not mediated by CYP3A4 – other interactions and effects that may occur with methylprednisolone are described below in Table 1.

Table 1 contains a list and description of pharmacological effects or interactions, with methylprednisolone, more common and/or clinically significant.

Table 1. Important effects/interactions of medications or substances with methylprednisolone

Type or Class of Drug - Drug or Substance	Interaction/effect
Anti-bacterial	CYP3A4 inhibitor. Methylprednisolone can

- Isoniazid	also increase the rate of acetylation and elimination of isoniazid.
Antibiotic, Antituberculous - Rifampicin	CYP3A4 inducer
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There were reported cases of increased or reduced effect from anticoagulants, when administered simultaneously with corticosteroids. In this way, the coagulation indices must be monitored in order to maintain the desired anticoagulant effects.
Anticonvulsants - Carbamazepine	CYP3A4 inducer (and substrate)
Anticonvulsants - Phenobarbital - Phenytoin	CYP3A4 inducer
Anticholinergics - Neuromuscular blockers	Corticosteroids can 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 agents (for additional information see section 4.4 Special warnings and precautions for use, musculoskeletal). 2 - Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction can be expected with all competitive neuromuscular blockers.
Cholinesterase inhibitors	Steroids may reduce the effects of cholinesterase inhibitors in myasthenia gravis.
Antidiabetics	Since corticosteroids can increase blood glucose concentrations, dose adjustments of antidiabetic medications may be necessary
Antiemetics - Aprepitant - Fosaprepitant	CYP3A4 inhibitors (and substrates)
Antifungals - 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 can induce the metabolism of HIV protease inhibitors, resulting in reduced plasmatic concentration levels.
Pharmacokinetic enhancer - Cobicistat	CYP3A4 inhibitor

Aromatase inhibitors - Aminoglutethimide	Adrenal suppression induced by aminoglutethimide may exacerbate endocrine changes caused by prolonged treatment with glucocorticoids
Calcium channel blockers - Diltiazem	CYP3A4 inhibitors (and substrates)
Contraceptives (oral) - Ethinylestradiol/norethindrone	CYP3A4 inhibitors (and substrates)
Grapefruit juice	CYP3A4 inhibitor
Immunosuppressants - Cyclosporine	CYP3A4 inhibitor (and substrate) 1) Mutual inhibition of metabolism occurs with the concomitant use of cyclosporine and methylprednisolone, which may increase plasma concentration of one or both medications. Therefore, it is possible that the adverse events associated to the use of each drug alone have greater probability of occurring in case of concomitant use. 2) Seizures have been reported with concomitant use of methylprednisolone and cyclosporine.
Immunosuppressants - Cyclophosphamide - Tacrolimus	CYP3A4 substrates
Macrolide antibacterials - Clarithromycin - Erythromycin	CYP3A4 inhibitors (and substrates)
Macrolide antibacterials - Troleandomycin	CYP3A4 inhibitor
NSAID - High doses of acetylsalicylic acid	1) There may be an increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are administered with NSAIDs. 2) Methylprednisolone may increase the clearance of high doses of acetylsalicylic acid, which can lead to decreased salicylate serum levels. Discontinuation of treatment with methylprednisolone can lead to an increased serum concentration of salicylates, which may lead to an increased risk of salicylates toxicity.
Potassium depleting agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e. diuretics), patients should be carefully observed regarding the development of hypokalaemia. There is also an increased risk of hypokalaemia with the concomitant use of corticosteroids with amphotericin B, xanthines or beta2 agonists.

Incompatibilities

To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate is administered separately from other substances administered intravenously. Physically incompatible substances in

solution with methylprednisolone sodium succinate include, but are not limited to: sodium allopurinol, doxapram hydrochloride, tigecycline, diltiazem hydrochloride, calcium gluconate, calcium bromide vecuronium, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol (see section 6.2 for more information).

4.6 Fertility, pregnancy and lactation

Fertility
Decreased fertility was observed in rats treated with corticosteroids (see section 5.3 Preclinical safety data).

Pregnancy
Animal studies have shown that administrating high corticosteroid doses to pregnant females may cause foetal malformations. However, corticosteroids do not appear to cause congenital malformations when given to pregnant women. Since no adequate human reproductive studies have been performed with methylprednisolone, this medicine should only be used during pregnancy after a careful assessment of the risk-benefit ratio for the mother and foetus.

Some corticosteroids cross the placenta easily. In a retrospective study, an increased frequency of low birthweight was observed in children whose mothers had been using corticosteroids. Although neonatal adrenal insufficiency is rare in infants that have been exposed to corticosteroids in the utero, infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be monitored carefully and examined for signs of adrenal insufficiency.

The effect of corticosteroids on delivery and labour is not known.

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

Breastfeeding
Corticosteroids are excreted in breast milk.

Corticosteroids excreted in breast milk can suppress the growth of breast-fed infants and disturb endogenous production of glucocorticoids. This medicine should only be used in lactating mothers only after a careful evaluation of the risk/benefit ratio to the mother and newborn

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 studied.
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

The following adverse reactions have been reported with the following contraindicated routes of administration - intrathecal/epidural: arachnoiditis, gastrointestinal disorder functional/ bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizures, sensory disturbances.

Within system organ classes, adverse reactions are listed by frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (<1/10 000); not known (cannot be estimated from the available data).

System organ class	Frequency	Undesirable effect
Infections and infestations	Common	Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs).
	Not known	Opportunistic infections, peritonitis*
Blood and lymphatic system disorders	Not known	Leucocytosis
Immune system disorders	Not known	Hypersensitivity to the drug (anaphylactic reaction and anaphylactoid reaction)
Endocrine disorders	Common	Cushingoid
	Not known	Suppression of the hypothalamic-pituitary-adrenal axis, steroid withdrawal syndrome
Metabolism and nutrition disorders	Common	Sodium retention, fluid retention
	Not known	Metabolic acidosis, glucose tolerance decreased, hypokalaemic alkalosis, dyslipidemia, increased insulin requirement (or oral hypoglicemic drugs in diabetics), increased appetite (which can lead to weight increase), epidural lipomatosis
Psychiatric disorders	Common	A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, drug dependence and suicidal thoughts). The following events were more common in children: mood swings, abnormal behaviour,

		insomnia, irritability
	Not known	Affective disorders (including affect lability, drug dependence, suicidal ideation), psychotic disorder (including mania, delirium, hallucination and schizophrenia [worsening]), confusional state, mental disorders, anxiety, personality change, mood swings, abnormal behaviour, insomnia, irritability
Nervous system disorders	Not known	Increase of intracranial pressure (with optical papilloedema of optical [benign intracranial hypertension]), seizures, amnesia, cognitive disturbances, dizziness, headache
Eye disorders	Common	Cataracts
	Not known	Exophthalmos, glaucoma, chorioretinopathy, vision blurred (see also section 4.4)
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Congestive heart failure (in susceptible patients), arrhythmia.
Vascular disorders	Common	Hypertension
	Not known	Thrombosis, hypotension, thrombotic events
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary embolism, hiccups
Gastrointestinal disorders	Common	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage)
	Not known	Gastric haemorrhage, intestinal perforation, pancreatitis, ulcerative oesophagitis, oesophagitis, abdominal pain, abdominal distension, diarrhoea, dyspepsia, nausea
Hepatobiliary disorders	Not known	Hepatitis, increase of liver enzymes
Skin and subcutaneous tissue disorders	Common	Ecchymosis, skin atrophy (thin fragile skin); Acne.
	Not known	Angioedema, petechiae, skin striae, skin hypopigmentation, hirsutism,

		rash, erythema, pruritus, urticaria, hyperhidrosis
Musculoskeletal and connective tissue disorders	Common	Growth retardation; Muscular Weakness, Osteoporosis
	Not known	Osteonecrosis, pathological fractures, muscle atrophy, myopathy, neuropathic arthropathy, arthralgia, myalgia
Reproductive system and breast disorders	Not known	Irregular menstruation
General disorders and administration site conditions	Common	Peripheral oedema, impaired wound healing
	Not known	Injection site reaction, fatigue, malaise
Investigations	Common	Blood potassium decreased
	Not known	Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase, increased intraocular pressure, decreased carbohydrate tolerance, increased urine calcium, suppression of reaction to skin tests, increased blood urea
Injury, poisoning and procedural complications	Not known	Tendon rupture (particularly of the Achilles tendon), spinal compression fracture

*peritonitis may be the first sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4)

Regarding fertility, existing data on animals is insufficient.

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids. Reports of acute toxicity and/or death following corticosteroid overdose are rare.
In the event of an overdose, no specific antidote is available; treatment is supportive and symptomatic, Methylprednisolone is dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for Systemic Use, ATC: H02AB04.

Methylprednisolone is a potent anti-inflammatory steroid, that has a greater anti-inflammatory power than prednisolone, and even less tendency than prednisolone to induce sodium and water retention.
Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory properties as methylprednisolone. When given parenterally and in equimolar quantities, the two drugs have equivalent biologic activity. The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, as indicated by a decrease in eosinophil count after intravenous administration, is at least four to one. This is in accordance with the relative potency of the oral formulations of methylprednisolone and hydrocortisone.

Methylprednisolone sodium succinate has been studied in acute spinal cord injury in two randomized, double-blind and comparative studies: "National Acute Spinal Cord Injury Studies" (NASCIS 2 and 3). The effect of a high dose of methylprednisolone sodium succinate, initially administered in a bolus dose of 30 mg/kg IV for 15 minutes, followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hour for 24 hours, was significant in neurological recovery when administered to patients up to 8 hours after the injury (NASCIS 2) and motor recovery was greater for patients which started between 3 hours and up to 8 hours after injury and which were 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 intramuscular administration of 40 mg of methylprednisolone sodium succinate to 14 healthy adult male volunteers, the mean peak concentration was 454 ng/ml, after one hour. At 12 hours, the plasma concentration of methylprednisolone decreased to 31.9 ng/ml. No methylprednisolone was detected 18 hours after its administration. Based on the area under the concentration versus time curve (AUC), the amount of drug absorbed by intramuscular administration was equivalent to that of the same dose when administered intravenously.

Results of a study shown that methylprednisolone sodium succinate ester is rapidly and extensively converted to the active metabolite of methylprednisolone after any of the administration routes. The extent of absorption of free methylprednisolone after IV and IM administration is equivalent and significantly superior to that obtained after administration of methylprednisolone oral solution or tablets. Once the extent of absorbed methylprednisolone after IV or IM treatment was equivalent, regardless of the amount of hemisuccinate ester that reached circulation after IV administration, it

appears that the ester is converted on the tissue following IM administration, with subsequent absorption of methylprednisolone in its free form.

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

Biotransformation
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 the CYP3A4 (for a list of drug interactions based on CYP3A4-mediated metabolism, see section 4.5 Interactions with other medicinal products and other forms of interactions).

Methylpredinosolone, 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.

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

Toxicities observed in repeat dose studies performed with methylprednisolone were consistent with the effects expected to occur with continued exposure to exogenous corticosteroids.

No genotoxicity or carcinogenicity studies with methylprednisolone were performed. The results of tests carried out with structurally similar substances do not indicate a risk of genotoxicity.

Corticosteroids have been shown to be teratogenic in many species when administered in doses equivalent to the human dose. In reproductive toxicity studies, glucocorticoids, such as methylprednisolone, have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-foetal lethality (e.g., increased reabsorption) and intrauterine growth retardation. Furthermore, they have shown adverse effects on male and female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium di-hydrogen phosphate dihydrate
Disodium phosphate anhydrous

Sodium hydroxide

The 40 mg vial also contains glucose.

6.2 Incompatibilities

To avoid compatibility problems with other drugs Methylprednisolone should be administered separately, only in the solutions mentioned in Section 6.6.

6.3 Shelf life

2 years

After reconstitution as recommended, use immediately, discard any remainder. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2º to 8ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

Store below 25°C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear glass vial with type I bromobutyl rubber stopper and flip-off aluminium cap.

Packs of 1 and 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

a) Preparation of solution for injection (reconstitution):

Methylprednisolone solution for injection should be prepared by dissolving the powder in an appropriate volume of water for injection, as shown in the table below.

Methylprednisolone presentation:	Solvent quantity (WFI):	Final solution concentration:
40 mg	1.2 ml	40 mg/ml
125 mg	2.1 ml	62.5 mg/ml
250 mg	4 ml	62.5 mg/ml
500 mg	8 ml	62.5 mg/ml
1000 mg	16 ml	62.5 mg/ml

b) Preparation of infusion solution

For intravenous infusion the initially prepared solution may be diluted with 5% dextrose in water for injection, 0.9% Sodium Chloride in water for injection (isotonic saline solution), or 5% dextrose in isotonic saline solution. To avoid compatibility problems with other drugs Methylprednisolone should be administered separately, only in the solutions mentioned.

Parenteral drugs 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.

Instructions to insert the needle on the rubber stopper:

To reduce the probability of rubber stopper fragmentation, and in accordance with European Pharmacopeia, it is recommended the use of a needle with an external diameter of 0.8mm (equivalent to a 21G) for the reconstitution of the product.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 15413/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/10/2018

10 DATE OF REVISION OF THE TEXT

20/05/2025