# 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 is indicated to treat any condition in which rapid and intense corticosteroid effect is required such as:

- Allergic states:

  Bronchial asthma

  Severe seasonal and perennial allergic rhinitis

  Angioneurotic oedema

  Anaphylaxis

- Dermatologic diseases:

  Severe erythema multiforme (Stevens-Johnson syndrome).

- Gastrointestinal diseases:

  Crohn's disease

  Ulcerative colitis.

- Neurological disorders:

  Acute exacerbations of multiple sclerosis superimposed on a relapsing-remitting background

  Secondary cerebral oedema caused by cerebal tumour

- Respiratory diseases:

  Aspiration of gastric contents

  Fulminat or disseminated pulmonary tuberculosis (with appropriate anti-tuberculosis chemotherapy)

- Miscellaneous:

  T.B.C. meningitis (with appropriate anti-tuberculosis chemotherapy)

  Transplantation

## 4.2 Posology and method of administration

Methylprednisolone may be administered intravenously or intramuscularly, the preferred method for emergency use being intravenous injection given over a suitable time interval.

Posology

When Methylprednisolone is administered in high doses intravenously, it should be given over a period of at least 30 minutes. Doses up to 250 mg should be given intravenously over a period of at least five minutes.

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

Adults

Dosage should be varied according to the severity of the condition, the initial dose should be between 10 to 500 mg. In the treatment of graft rejection reactions following transplantation, a dose of up to 1 g/day may be required. Although doses and protocols have varied in studies using 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 hours period until the patient's condition has stabilized, as prolonged high dose corticosteroid therapy can cause serious corticosteroid induced side effects (see Sections 4.4 and 4.8).

Paediatric population

In the treatment of high dose indications, such as haematological, rheumatic, renal and dermatological conditions, a dosage of 30 mg/kg/day to a maximum of 1 g/day is recommended. This dosage may be repeated in three consecutive cycles on a daily basis or on every second day. In the treatment of graft rejection reactions following transplantation, a dosage of 10 to 20 mg/kg/day for up to 3 days, to a maximum of 1 g/day, is recommended. In the treatment of asthmatic states, a dosage of 1 to 4 mg/kg/day for 1 - 3 days is recommended.

Elderly patients:

Methylprednisolone 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 Section 4.4).

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 (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 is capable of providing relief of symptoms within half to two hours. In patients with status asthmaticus Methylprednisolone may be given at a dose of 40 mg intravenously, repeated as dictated by the patient response. In some asthmatic patients it may be of advantage to administer the product as a slow drop infusion over a time period of several hours.

In graft rejection reactions following transplantation doses of up to 1 g per day have been used to suppress rejection crises. In case of acute rejection, doses of 500 mg to 1 g are commonly used. Treatment should be continued only until the patient's condition has stabilized; 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 malignant diseases may need to remain on oral corticosteroid therapy for months or even life. Similar or higher doses may be helpful to control cerebral 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 A** [2] | **Dose (mg)** | **Route** | **Interval in hours** | **Days 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 |

(1) Fox JL, MD. "Use of Methylprednisolone in Intracranial Surgery" Medical Annals of the District of Columbia, 34:261 265, 1965.

(2) Cantu RC, MD Harvard Neurological Service, Boston, Massachusetts. Letter on file, The Upjohn Company (February 1970).

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 1 g daily for 3 days. Methylprednisolone 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.

For instruction on reconstitution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

The usual contra-indications to the systemic or local use of corticosteroids should be observed. Methylprednisolone is contra-indicated in systemic fungal infection and in systemic infection unless specific anti-infective therapy is employed. For intrathecal administration, since reports of severe medical events have been associated with this route of administration. Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

Cerebral oedema associated with malaria.

## 4.4 Special warnings and precautions for use

*Special warnings*

- Undesirable effects may be minimised by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity (see Section 4.2).

- Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute rebound exacerbation of disease, acute adrenal insufficiency or polyarteritis, being tapered off over weeks or months according to the dose and duration of treatment. During prolonged therapy any inter-current illness, trauma, anaesthesia or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

  Abrupt withdrawal of systemic corticosteroid treatment, which has been applied for a time period of maximum 3 weeks is appropriate if the treating physician considers a

relapse of the disease to be unlikely. Abrupt withdrawal of doses up to 32 mg daily of methylprednisolone for maximum 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 treatment lasting 3 weeks or less:

  - Patients who have received repeated courses of systemic corticosteroid treatment, particularly if applied for longer 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 receiving repeated doses in the evening.

- Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

- Because rare instances of anaphylactic reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of drug allergy.

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

- Varicella is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive 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.

- 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 Section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

- Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults, particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IVIG) may be indicated. Exposed patients should be advised to seek medical advice without delay.

- Administration of live or live, attenuated vaccines is contra-indicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

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

- Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see Section 4.8 Undesirable effects). There are reports of cardiac arrhythmias, and/or circulatory collapse, and/or cardiac arrest following the rapid administration of large intravenous doses of Methylprednisolone (more than 0.5 g administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, Methylprednisolone and may be unrelated to the speed or duration of infusion.

- Prolonged use of corticosteroids may produce posterior sub-capsular cataracts and nuclear cataracts (particularly in children) and glaucoma with possible damage to the optic nerve. Frequent ophthalmic monitoring is necessary.

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

- Data from a clinical study conducted to establish the efficacy of Methylprednisolone in septic shock, suggest that a higher mortality occurred in the sub-sets of patients who entered the study with elevated serum creatinine levels or who developed a secondary infection after Methylprednisolone therapy was begun.

- Intramuscular injection should avoid the deltoid area because of the possibility of tissue atrophy.

- Methylprednisolone should not be used routinely to treat head injury as demonstrated by the results of a multicentre study. The study results revealed an increased mortality in the 2 weeks after injury in patients administered Methylprednisolone compared to placebo (1.18 relative risk). A causal association with methylprednisolone sodium succinate treatment has not been established.

- 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.

- **Immune System Effects**
-
- Cow's milk allergy (the following paragraphs only apply to Methylprednisolone 40 mg.)
- Methylprednisolone 40 mg contains lactose produced from bovine origin as an excipient and may therefore contain trace amounts of cow's milk proteins (the allergens of cow's milk). Serious allergic reactions, including bronchospasm and anaphylaxis, were reported in patients allergic to cow's milk proteins who were treated for acute allergic conditions. Patients with known or suspected allergy to cow's milk must not be administered Methylprednisolone 40 mg (see section 4.3).
- Allergic reactions to cow's milk proteins should be considered in patients receiving Methylprednisolone 40 mg for the treatment of acute allergic conditions in whom symptoms worsen or who are presenting new allergic symptoms (see section 4.3). Administration of Methylprednisolone 40 mg should be stopped, and the patient's condition should be treated accordingly.

*Special precautions*

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

- Osteoporosis (post-menopausal females are particularly at risk).
- Hypertension or congestive heart failure.
- Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.
- Diabetes mellitus (or a family history of diabetes).
- History of tuberculosis.
- Glaucoma (or a family history of glaucoma).
- Previous corticosteroid-induced myopathy.
- Liver failure or cirrhosis.
- Renal insufficiency.
- Epilepsy.
- Active or latent peptic ulceration.
- Fresh intestinal anastomoses.
- Thrombosis including venous thromboelism 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.
- Abscess or other pyogenic infections.
- Ulcerative colitis.
- Diverticulitis.
- An acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.
- Ocular herpes simplex, for fear of corneal perforation.
- Hypothyroidism.
- Cushing's Syndrome.
- Exanthematous infectious diseases.
- Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Visual disturbance

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.

Scleroderma renal crisis

Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more

prednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

Paediatric population
Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimise suppression of the hypothalamo-pituitary-adrenal axis and growth retardation, treatment should be administered where possible as a single dose on alternate days.

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. Close clinical supervision is required to avoid life-threatening reactions.

## 4.5 Interaction with other medicinal products and other forms of interaction

Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse events associated with the individual use of either drug may be more apt to occur.

Immunosuppressants, as methotrexate, may have synergistic effect on disease state which may allow to reduce dose of corticosteroid.

Drugs that induce hepatic enzymes, such as rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced. It may be necessary to increase the Methylprednisolone dose to achieve the desired response.

Drugs that inhibit the cytochrome P450 enzymatic system (particularly CYP3A4), such as erythromycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of methylprednisolone should be titrated to avoid steroid toxicity.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Steroids may reduce the effects of anticholinesterases in myasthenia gravis. The desired effects of hypoglycaemic agents (including insulin), anti-hypertensive and diuretic drugs are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in hypothrombinaemia.

Steroids have been reported to interact with neuromuscular blocking agents such as pancuronium with partial reversal of the neuromuscular block.

Antipsychotics can cause recurrence or poor control of CNS symptoms, when used with methylprednisolone, which may require a dose adjustment.

Sympathomimetic agents, as salbutamol, can increase the efficacy and potentially increase toxicity by increased response to sympathetic agents, when used with methylprednisolone.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies have shown that high corticosteroid doses to pregnant females may cause foetal malformations. However, corticosteroids do not appear to cause congenital malformations when given to pregnant women. Despite this, methylprednisolone sodium succinate should be used during pregnancy in critical cases only as studies in humans cannot establish the safety of the product during use in pregnancy.

Some corticosteroids cross the placenta easily. In a retrospective study, an increased frequency of low birth-weight was observed in children whose mothers had been using corticosteroids. Although adrenal insufficiency is rare in children who have been exposed to corticosteroids in utero, children exposed to high corticosteroid doses should be monitored carefully and examined for the risk of adrenal insufficiency.

The effect of corticosteroids on delivery is not known.

Cataract has been observed in neonates whose mothers have received long-term corticosteroid treatment 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. As reproduction studies with corticosteroids in humans are inadequate, corticoids should be used in lactating mothers only if the benefit from the treatment is assessed greater than the possible risks to the child.

The possible benefits of corticosteroid medication must be weighed against possible adverse effects to the mother and embryo or foetus before giving this medicinal product to pregnant or lactating women, or to women of fertile age.

Fertility
There is no evidence that corticosteroids would impair fertility.

## 4.7 Effects on ability to drive and use machines

The effect of Methylprednisolone 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 therapy would be considered as short term. However, the possibility of side effects attributable to corticosteroid therapy should be recognised, particularly when high dose therapy is being used (see Section 4.4). Such side-effects include:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

| **System organ class:** | **Undesirable effect:** |
|---|---|
| Infections and infestations | Frequent: Infections<br>Unknown: Oportunistic infections |
| Blood and lymphatic system disorders | Unknown: leucocytosis, thrombo-embolism |
| Immune system disorders | Unknown: anaphylactic reaction with or without circulatory collapse, cardiac arrest, bronchospasm, cardiac arrhythmias, hypotension or hypertension. |
| Endocrine disorders | Frequent: Cushingoid facies<br>Unknown: Suppression of the hypothalamo- |

| | |
|---|---|
| | pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea., hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, manifestations, negative nitrogen and calcium balance. Increased appetite. |
| Metabolism and nutrition disorders | Frequent: sodium and water retention,<br>Unknown: hypokalaemic alkalosis, metabolic acidosis, potassium loss, reduced tolerance to glucose, need to increase the dosage of insulin or oral hypoglicemic drugs in diabetic patients, increased appetite, epidural lipomatosis |
| Psychiatric disorders | Frequent: a wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood psychological dependence and suicidal thoughts)<br>Unknown: psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, seizures and 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 5-6%. Psychological effects have been reported on withdrawal of corticosteroids. Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of methylprednisolone. |
| Nervous system disorders | Unknown: Seizures, increase of intracranial pressure (with oedema of optical papilla [intracranial benign hypertension]), amnesia, cognitive disturbances, dizziness, headache |
| Eye disorders | Frequent: subcapsular cataracts<br>Unknown: increased intra-ocular pressure, glaucoma, papilloedema, exophthalmos, glaucoma, exoftalmia, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease, chorioretinopathy, Vision, blurred (see also section 4.4). |

| | |
|---|---|
| Ear and labyrinth disorders | Unknown: vertigo |
| Cardiac disorders | Unknown: congestive heart failure in susceptible patients, myocardial rupture following a myocardial infarction, arrhythmia. |
| Vascular disorders | Frequent: hypertension<br>Unknown: hypotension, thrombotic events |
| Respiratory, thoracic and mediastinal disorders | Unknown: persistent hiccups with high doses of corticsteroids. |
| Gastrointestinal disorders | Frequent: peptic ulceration possibly with perforation and haemorrhage, gastric haemorrhage,<br>Unknown: dyspepsia, abdominal distension, oesophageal ulceration, oesophageal candidiasis, oesophagitis, perforation of the bowel, acute pancreatitis. Nausea, vomiting and bad taste in mouth may occur especially with rapid administration. |
| Hepatobiliary disorders | Unknown: increases in alanine transaminase (ALT, SGPT) aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid 13 treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation. Hepatitis, increase of liver enzymes |
| Skin and subcutaneous tissue disorders | Frequent: skin atrophy, acne<br>Unknown: erithema, angioedoema, pruritus, petechiae and ecchymosis, skin thinning, bruising, striae, telangiectasia, hirsutism. |
| Musculoskeletal and connective tissue disorders | Frequent: muscle weakness, retarded growth<br>Unknown: steroid myopathy, osteoporosis, vertebral and long bone fractures, artralgia, avascular osteonecrosis, tendon rupture. |
| Renal and urinary disorders | Unknown: Scleroderma renal crisis* |
| Reproductive system and breast disorders | Unknown: irregular menstruation |
| General disorders and administration site conditions | Frequent: impaired healing<br>Unknown: fatigue, malaise, a 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight. Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. |

*Scleroderma renal crisis

Amongst the different subpopulations the occurrence of scleroderma renal crisis varies. The highest risk has been reported in patients with diffuse systemic sclerosis. The lowest risk has been reported in patients with limited systemic sclerosis (2%) and juvenile onset systemic sclerosis (1%)

**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 at: www.mhra.gov.uk/yellowcard.

### 4.9 Overdose

Reports of acute toxicity and metabolic disturbances with glucocorticoids are rare but do occur. There is no clinical syndrome of acute overdosage with Methylprednisolone. Acute overdose may possibly aggravate pre-existing disease states such as ulceration of the gastrointestinal tract, electrolyte disturbances, infections, diabetes and oedema. Repeated high doses of methylprednisolone have caused hepatic necrosis and an increase in amylase. Bradyarrhythmias, ventricular arrhythmias and cardiac arrest have been observed in cases of intravenous administration of high doses of methylprednisolone.
Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state. The possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. In the event of an overdose, no specific antidote is available; treatment is symptomatic and supportive, including respiratory and cardiovascular function. In chronic toxicity, fluids and electrolytes should be monitored closely. Serum levels are not clinically useful. Methylprednisolone is dialysable.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties
Pharmaco-therapeutic group: Corticosteroids for Systemic Use; ATC: H02AB04.

Methylprednisolone is a potent anti-inflammatory steroid. It has a greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention. Its anti-inflamatory activity is at least five times that of hydrocortisone.

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is

at least four to one. This is in good agreement with the relative oral potency of methylprednisolone and 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.

***Absorption***

After an intravenous infusion of Methylprednisolone, 30mg/kg over a 20 minute period or 1g over 30 to 60 minutes, peak methylprednisolone plasma concentrations of approximately 20µg/ml were achieved. Peak methylprednisolone levels of 42-47µg/100ml were reported following a single 40mg IV bolus injection to six adult male volunteers

Methylprednisolone is extensively bound to plasma proteins, mainly to globulin and less so to albumin. Only unbound corticosteroid has pharmacological effects or is metabolised. Metabolism occurs in the liver and to a lesser extent in the kidney. Metabolites are excreted in the urine.

Peak methylprednisolone plasma levels of 33.67 µg/100ml were achieved in two hours after a single 40 mg IM injection to 22 adult male volunteers. Although with intramuscular (IM) injection lower peak levels are obtained than with intravenous (IV) injection, the plasma levels persist longer such that the extent of methylprednisolone absorption is equivalent with either route of administration.

***Distribution***

Methylprednisolone is widely distributed throughout the body and is described by a two-compartment model. Its apparent volume of distribution is approximately 1.4 ml/kg and its total clearance is approximately 5 to 6ml/min/kg.

Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.

Methylprednisolone readily crosses the blood-brain barrier into the central nervous system with peak CSF levels being 5 - 6% of the corresponding plasma levels.

Methylprednisolone peak CSF levels occurred within five minutes to one hour after IV administration of a 500 mg dose to patients with lupus cerebritis.

Methylprednisolone and its sodium succinate salt cross the placental barrier. Although there is no data regarding methylprednisolone passage into breast milk of humans, it is present in breast milk of animals.

***Biotransformation***

Methylprednisolone, the sodium succinate ester of methylprednisolone, is rapidly and extensively hydrolysed *in vivo* by cholinesterases to free methylprednisolone. In humans, methylprednisolone is metabolised in the liver to inactive metabolites, the major ones being 20β-hydroxymethylprednisone and 20 α-hydroxy-6-amethylprednisone. Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4-mediated metabolism (see Section 4.5).

***Elimination***

The mean elimination half-life ranges for total methylprednisolone is in the range of 1.8 to 5.2 hours.

The plasma protein binding of methylprednisolone in humans is approximately 77%. Total body clearance following intravenous or intramuscular injection of methylprednisolone to healthy adult volunteers is approximately 15 – 16l/hr. In adult volunteers receiving 40 mg Methylprednisolone, either IM or IV, renal clearance is 0.61 - 0.83l/hr. Methylprednisolone clearance is altered by concurrent administration of troleandomycin, erythromycin, rifampin, anti-convulsants, and theophylline.

Following IV administration of radiolabelled 6α-methyl-prednisolone to six cancer patients, 75% of total reactivity was recovered in the urine after 96 hours and 9% in the faeces after five days. Twenty percent of the total dose was excreted in the bile, but the time course was not cited.

## 5.3 Preclinical safety data

Non-clinical data reveal no unexpected hazards for mice, rats, rabbits and dogs based on conventional studies of safety pharmacology and repeated dose toxicity with intravenous, intraperitoneal, subcutaneous, intramuscular, and peroral administration.

Methylprednisolone is a potent steroid the pharmacological effects of which are comparable to those of glucocorticoids, including the effects on carbohydrate metabolism, electrolyte and fluid balance, blood cells, lymphatic tissue and protein

metabolism, which can lead to reduction or cessation of weight gain, lymphopenia, and atrophy of the spleen, thymus, lymph nodes, adrenal cortex and testes as well as fatty liver, and hyperplasia of pancreatic islet cells. A 30 day study on reversibility in rats which had received methylprednisolone showed that the vital functions returned to normal after about 1 month from discontinuing the drug. Following a 52-week-long administration of methylprednisolone suleptanate to rats, many parameters returned to normal after a 9 week period of reversibility. Toxicities detected in studies with repeated dosage are those that can be expected after continuous exposure to exogenous adrenocortical steroids.

Carcinogenicity

No long-term studies in animals have been done to assess carcinogenicity as the drug substance is meant for short-term use only, and no signs of a carcinogenic effect have been detected. There is no evidence of carcinogenicity of corticosteroids.

Mutagenicity

In DNA damage determination by the alkaline elution technique in V79 cells of the Chinese hamster, no evidence on genetic or chromosomal mutations was obtained. Methylprednisolone did not cause chromosomal damage without the hepatic activation system.

Reproduction toxicity

No teratogenic effects in mice or rats were detected in animal studies on embryotoxic effects of methylprednisolone at the intraperitoneal daily dose of 125 mg/kg/day to mice and 100 mg/kg/day to rats. In rats, methylprednisolone was teratogenic when less than 20 mg/kg/day was given subcutaneously. Methylprednisolone aseponate was teratogenic in rats when less than 1.0 mg/kg/day was given subcutaneously.

Animal data are insufficient with respect to 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 Hikma presentation: | Solvent quantity (WFI): | Quantity of dissolved product: | Final solution concentration: |
|---|---|---|---|
| 40 mg | 1.2 ml | 1 ml | 40 mg/ml |
| 125 mg | 2.1 ml | 2 ml | 62.5 mg/ml |
| 250 mg | 4 ml | 4 ml | 62.5 mg/ml |
| 500 mg | 8 ml | 8 ml | 62.5 mg/ml |
| 1000 mg | 16 ml | 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.

## 7 MARKETING AUTHORISATION HOLDER

Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó 8, 8A e 8B – Fervença
2705-906 Terrugem
Portugal
portugalgeral@hikma.com

## 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

21/10/2018