Summary of Product Characteristic

1. Name of the Medicinal Product

1.1 Product Name

M-prednisolone

1.2 Strength

1 g, 2 g

1.3 Pharmaceutical Dosage Form

Powder for solution for injection

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Methylprednisolone sodium succinate

2.2 Quantitative Declaration:

Each vial contains:-

Methylprednisolone (as Methylprednisolone sodium succinate 1.367 g)	1 g
Methylprednisolone (as Methylprednisolone sodium succinate 2.734 g)	2 g

3. Pharmaceutical Form

White to off-white sterile powder for injection

4. Clinical Particulars

4.1 Therapeutic indications

- Endocrine disorders:
  - primary or secondary adrenocortical insufficiency (in conjunction with mineralocorticoids, where applicable);
  - acute adrenocortical insufficiency (mineralocorticoid supplementation may be necessary);
  - shock secondary to adrenocortical insufficiency, or shock unresponsive to conventional therapy when adrenocortical insufficiency may be present (when mineralocorticoid activity is undesirable);
  - preoperatively or in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful;
  - congenital adrenal hyperplasia;
  - non-suppurative thyroiditis;
  - hypercalcemia associated with cancer.

- Rheumatic disorders (as adjunctive therapy for short-term administration in the management of an acute episode or exacerbation)
    - posttraumatic osteoarthritis;
    - synovitis of osteoarthritis;
    - rheumatoid arthritis, including juvenile rheumatoid arthritis;
    - acute and subacute bursitis;
    - epicondylitis;
    - acute nonspecific tenosynovitis;
    - acute gouty arthritis;
    - psoriatic arthritis;
    - ankylosing spondylitis.
- Collagen diseases and immune complex diseases (during an exacerbation or as maintenance therapy in selected cases)
    - systemic lupus erythematosus;
    - acute rheumatic carditis.
    - systemic dermatomyositis (polymyositis);
- Dermatologic disease:
    - pemphigus;
    - severe erythema multiforme (Stevens-Johnson syndrome);
    - exfoliative dermatitis;
    - severe psoriasis;
    - bullous dermatitis herpetiformis;
    - severe seborrheic dermatitis;
    - mycosis fungoides.
- Allergic states (to control severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment)
    - bronchial asthma;
    - contact dermatitis;
    - atopic dermatitis;
    - serum sickness;
    - seasonal or perennial allergic rhinitis;
    - drug hypersensitivity reactions;

- urticarial transfusion reaction;
- acute noninfectious laryngeal edema.

- Ophthalmic diseases (severe acute and chronic allergic and inflammatory processes involving the eye)
  - herpes-zoster ophthalmicus;
  - iritis, iridocyclitis;
  - chorioretinitis;
  - diffuse posterior uveitis and choroiditis;
  - optic neuritis;
  - sympathetic ophthalmia;
  - anterior segment inflammation;
  - allergic conjunctivitis;
  - allergic corneal marginal ulcers;
  - keratitis.
- Gastrointestinal diseases (to manage critical period of the disease)
  - ulcerative colitis;
  - regional enteritis.
- Respiratory disease
  - Symptomatic sarcoidosis;
  - berylliosis;
  - fulminating or disseminated tuberculosis (when used concurrently with appropriate antituberculous chemotherapy);
  - Loeffler's syndrome not manageable by other means;
  - aspiration pneumonitis;
  - moderate to severe *Pneumocystis jiroveci* pneumonia in AIDS patients (as adjunctive therapy when given within the first 72 hours of initial anti-pneumocystis treatment);
- Hematologic disorders
  - acquired (autoimmune) hemolytic anemia;
  - idiopathic thrombocytopenic purpura in adult;
  - secondary thrombocytopenia in adults;
  - erythroblastopenia (RBC anemia);
  - congenital (erythroid) hypoplastic anemia.
- Neoplastic diseases (palliative management)

- leukemias and lymphomas in adults;
- acute leukemia of childhood;

- Edematous states
  - To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia.
- Nervous System
  - acute exacerbations of multiple sclerosis;
- Other indications
  - tuberculous meningitis with subarachnoid block or impending block (when used concurrently with appropriate chemotherapy);
  - trichinosis with neurologic or myocardial involvement;

4.2 Posology and method of administration

Posology

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

Table: Recommended dosages for methylprednisolone sodium succinate

Indication	Dosage
Adjunctive therapy in life-threatening conditions	Administer 30 mg/kg IV over a period of at least 30 minutes. Dose may be repeated every 4 to 6 hours for up to 48 hours.
Rheumatic disorders unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates. 1g/day for 1 to 4 days, or 1 g/month for 6 months
Systemic lupus erythematosus unresponsive to standard therapy (or during exacerbation episodes)	Administer 1g/day for 3 days as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates.
Multiple sclerosis unresponsive standard therapy (or during exacerbation episodes)	Administer 1g/day for 3 or 5 days as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's

	condition dictates.
Edematous states, such as glomerulonephritis or lupus nephritis, unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within 1 week after therapy, or as the patient's condition dictates. 30 mg/kg every other day for 4 days, or 1g/day for 3, 5 or 7 days.
Terminal cancer (to improve quality of life)	Administer 125 mg/day IV for up to 8 weeks.
Prevention of nausea and vomiting associated with cancer chemotherapy	*For mild to moderately emetogenic chemotherapy:* Administer 250 mg IV over least 5 minutes 1 hour before start of chemotherapy. Repeat dose of methylprednisolone at the initiation of chemotherapy and at the time of discharge. A chlorinated phenothiazine may also be used with the first dose of methylprednisolone for increased effect. *For severely emetogenic chemotherapy:* Administer 250 mg IV over at least 5 minutes with appropriate doses of metoclopramide or a butyrophenone 1 hour before start of chemotherapy. Repeat dose of methylprednisolone at the initiation of chemotherapy and at the time of discharge.
Acute spinal cord injury	*Treatment should begin within 8 hours of injury.* For patients initiated on treatment within 3 hours of injury: Administer 30 mg/kg as an IV bolus over a 15-minute period, followed by a 45-minute pause, and then a continuous IV infusion of 5.4 mg/kg/h for 23 hours For patients initiated on treatment within 3 to 8 hours of injury: Administer 30 mg/kg as an IV bolus over a 15- minute period, followed by a 45-minute pause, and then a continuous IV infusion of 5.4 mg/kg/h for 47 hours. There should be a separate intravenous site for the infusion pump.
Pneumocystis jiroveci pneumonia in	*Therapy should begin within 72 hours of initial anti-*

patients with AIDS	*pneumocystis treatment.* One possible regimen is to administer 40 mg IV every 6 to12 hours with gradual tapering over a maximum of 21 days or until the end of pneumocystis therapy. Due to the increased rate of reactivation of tuberculosis in AIDS patients, consideration should be given to the administration of antimycobacteria therapy if corticosteroids are used in this high risk group. The patient should also be observed for activation of other latent infections.
As adjunctive therapy in other indications	Initial dose will vary from 10 to 500 mg IV, depending on the clinical condition. Larger doses may be required for short-term management of severe, acute conditions. Initial doses up to 250 mg should be administered IV over a period of at least 5 minutes, while lager doses should be administered over at least 30 minutes. Subsequent doses may be administered IV or IM at intervals dictated by the patient's response and clinical condition.

Mode of Administration

Administration: The route of administration depends on the condition being treated and the response of the patient. Methylprednisolone sodium succinate may be administered by intravenous (IV) injection or infusion, or by intramuscular (IM) injection. The preferred method for Initial emergency use is IV injection.

Rate of administration

Rate dependent upon dose. Do not administer large doses IV push. Severe adverse effects have been reported in patients receiving large doses (>500 mg) over <10 minutes. Administer large doses over at least 30 minutes.

To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate be administered separately from other drugs whenever possible, as either IV push, through an IV medication chamber, or as an IV "piggy-back" solution.

4.3 Contraindication

Methylprednisolone sodium succinate is contraindicated:

- In patients who have systemic fungal infections.
- In patients with known hypersensitivity to methylprednisolone or any component of the formulation.

- For use by the intrathecal route of administration.
- For use by the epidural route of administration.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive dose of corticosteroid.

4.4 Special warning and precautions for use

Warnings based on Thai Ministry of Public Health Announcement

- Do not use in patient with gastrointestinal disease, diabetes, tuberculosis and viral infection.

Warnings/ precautions

Immunosuppressant Effects/Increased Susceptibility to Infections

Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize 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 infections complications increases.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, 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. Kill 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 appropriate antituberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission. The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental

corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short-course, high-dose corticosteroids did not support their use. However, meta-analyses, and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor dependent septic shock.

Immune System Effects

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

Endocrine Effects

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

Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy. This effect may be minimized by use of alternate-day therapy. In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

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

Metabolism and Nutrition

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

Psychiatric Effects

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknow. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Nervous System Effects

Corticosteroids should be used with caution in patients with seizure disorders. Corticosteroids should be used with caution in patients with myasthenia gravis. Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

Severe medical events have been reported in association with the intrathecal/epidural routes of administration

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

Ocular Effects

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible 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. Corticosteroids therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

Cardiac Effects

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy.

There are reports of cardiac arrhythmias, and/or circulatory collapse, and/or cardiac arrest following the rapid administration of large intravenous 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 the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed or duration of infusion. Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

Vascular Effect

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. Steroids should be used with caution in patients with hypertension.

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 hemorrhage may occur without significant pain. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

Corticosteroids should be used with caution in patients with non-specific ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary Effects

High doses of corticosteroids may produce acute pancreatitis.

Drug-induced liver injury such as acute hepatitis can result from cyclical pulsed IV methylprednisolone (usually at doses of 1 gm/day). The time to onset of acute hepatitis can be several weeks or longer. Resolution of the adverse event has been observed after treatment was discontinued.

Musculoskeletal Effects

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

Renal and Urinary Disorders

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

Investigations

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

Injury, poisoning and procedural complications

Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury; a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

Other

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/ benefit decision must be made in each individual case as to dose and duration of treatment as to whether daily or intermittent therapy should be used. 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. Aspirin and non-steroidal anti-inflammatory agents should be used cautiously in conjunction 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 identified pheochromocytoma after an appropriate risk/ benefit evaluation.

Use in children

The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in associated with the “gasping syndrome” the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and use of such regimen should be restricted to the most urgent indications. Alternate-day glucocorticoid therapy usually 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.

4.5 Interaction with other medicinal products and other forms of interactions

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthesis corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

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

CYP3A4 inducer – drug that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Co-administration may require an increase in methylprednisolone dosage to achieve the desired result.

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

Non-CYP3A4-medicated effects – other interactions and effects that occur with methylprednisolone are described in table below.

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

Drug Class or Type Drug or Substance	**Interaction/ Effect**
Antibacterial - Isoniazid	CYP3A4 inhibitors. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - Rifampin	CYP3A4 inhibitors
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulant is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - Carbamazepine	CYP3A4 inducer (and substrates)

Anticonvulsants - Phenobarbital - Phenytoin	CYP3A4 inducer
Anticholinergics - Neuromuscular blockers	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. 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.
Acetylcholinesterase	Steroids may reduce the effects of Acetylcholinesterase in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required
Antiemetic - Aprepitant - Fosaprepitant	CYP3A4 inhibitor (and substrates)
Antifungal - Itraconazole - Ketoconazole	CYP3A4 inducer (and substrates)
Antivirals - HIV-Protease Inhibitors	CYP3A4 inducer (and substrates). 1) Proteases inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase Inhibitors - Aminoglutethimide	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - Diltiazem	CYP3A4 inhibitor (and substrates)
Contraceptive (oral)	CYP3A4 inhibitor (and substrates)

- Ethinylestradiol/ Norethindrone	
Grapefruit juice	CYP3A4 inhibitor
Immunosuppressant - Cyclosporine	CYP3A4 inhibitor (and substrates) 1) Mutual inhibitor of metabolism occurs with concurrent use of cyclosporine 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 co-administration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine.
Immunosuppressant - Cyclophosphamide - Tacrolimus	CYP3A4 substrates
Macrolide Antibacterial - Clarithromycin - Erythromycin	CYP3A4 inhibitor (and substrates)
Macrolide Antibacterial - Troleandomycin	CYP3A4 inhibitor
NSAIDs (non-steroidal 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, with can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to an increased risk of salicylate toxicity.
Potassium depleting agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics) patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonist.

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 not limited to: allopurinol sodium doxapram hydrochloride, tigecycline, diltiazem hydrochloride, calcium gluconate, vecuronium bromide, rocurocium bromide, cisatracurium besylate, glycopyrrolate, propofol.

4.6 Pregnancy and lactation

Animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformation. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women. Nevertheless, because the studies in humans cannot rule out the possibility of harm, methylprednisolone sodium succinate should be used during pregnancy only if clearly needed.

Some corticosteroids readily cross the placenta. One retrospective study found an increase incidence of low-birth weight in infants born of mother receiving corticosteroids. Infants born to mother, who have receiving substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency, although neonatal adrenal insufficiency appears to be rare in infants who were exposed in utero to corticosteroids. There are no known effects of corticosteroids on labor and delivery. Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy. Benzyl alcohol can cross the placenta.

Lactation: Corticosteroids are excreted in breast milk. Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risks to the infant.

4.7 Effects on ability to drive and use machine

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

The following adverse reactions have been reported with the following contraindicated routes of administration: intrathecal/epidural: arachnoiditis, functional gastrointestinal disorder/ bladder dysfunction, headache, meningitis, parapareisis/ paraplegia, convulsions, sensory disturbances. The frequency of these adverse reactions is not known.

System Organ Class (MedDRA)	**Frequency not known (cannot be estimate from the available data)**

Infections and infestations	Opportunistic infection; infection
Blood and lymphatic system disorders	Leukocytosis
Immune system disorders	Drug hypersensitivity (including anaphylactic reaction and anaphylactoid reaction)
Endocrine disorders	Cushingoid; hypopituitarism; steroids withdrawal syndrome
Metabolism and nutrition disorders	Lipomatosis; sodium retention; fluid retention; alkalosis hypokalemic; dyslipidemia; glucose tolerance impaired; increased (or oral hypoglycemic agents in diabetics); nitrogen balance negative (due to protein catabolism); blood urea increased; increased appetite (which may result in weight increased)
Psychiatric disorders	Affective disorder (including depressed mood, euphoric mood, affect lability, drug dependence, suicidal ideation); psychotic disorder (including mania, delusion, hallucination, and schizophrenia); mental disorder; personality change; confusional state; anxiety; mood swings; abnormal behaviour; insomnia; irritability.
Nervous system disorders	Epidural lipomatosis; intracranial pressure increased (with papilloedema [benign intracranial hypertension]); convulsion; amnesia; cognitive disorder; dizziness; headache
Eye disorders	Central serous chorioretinopathy; cataract; glaucoma; exophthalmos
Ear and labyrinth disorders	Vertigo
Cardiac disorder	Cardiac failure congestive (in susceptible patients); arrhythmia
Vascular disorders	Thrombosis; hypertension; hypotension
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism; hiccups
Gastrointestinal disorders	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage); intestinal perforation; gastric haemorrhage; pancreatitis; peritonitis; oesophagitis ulcerative; oesophagitis; abdominal distention; abdominal pain; diarrhoea; dyspepsia; nausea.
Hepatobiliary disorders	Hepatitis**
Skin and subcutaneous tissue disorders	Angioderma; oedema peripheral; hirsutism; petechiae; ecchymosis; skin atrophy; erythema; hyperhidrosis; skin striae, rash, pruritus; urticaria; acne; skin hypopigmentation

Musculoskeletal and connective tissue disorders	Muscle weakness; myalgia; myopathy; muscle atrophy; osteoporosis; osteonecrosis; pathological fractures; neuropathic arthropathy; arthralgia; growth retardation.
Reproductive system and breast disorders	Menstruation irregular
General disorders and administration site conditions	Impaired healing; fatigue; malaise; injection site reaction
Investigations	Urine calcium increased; blood potassium decreased; carbohydrate tolerance decreased; intraocular pressure increased; alanine aminotransferase increased; aspartate aminotransferase increased; blood alkaline phosphatase increased; suppression; of reactions to skin tests*
Injury, poisoning and procedural complications	Spinal compression fracture; tendon rupture

*Not a MedDRA PT

** Hepatitis has been reported with IV administration

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 dialyzable.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention.

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methyl prednisolone. 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.

5.2 Pharmacokinetic properties

Methylprednisolone pharmacokinetic is linear, independent of route of administration.

Absorption: after a 40 mg intramuscular dose of methylprednisolone sodium succinate to fourteen healthy adult male volunteers, the average peak concentration of 454 ng/mL was achieved at 1 hour. At 12 hours, the

methylprednisolone plasma concentration has declined to 31.9 ng/mL. No methylprednisolone was detected 18 hours after dosing. Based on area-under-the-time-concentration curve, an indication of total drug absorbed, intramuscular methylprednisolone sodium succinate was found to be equivalent to the same dose administered intravenously. Results of study demonstrated that the sodium succinate ester of methylprednisolone is rapidly and extensively converted to the active methylprednisolone moiety after all routes of administration. Extent of absorption of free methylprednisolone following IV and IM administrations were found to be equivalent and significantly greater than those following administration of the oral solution and oral methylprednisolone tablets. Since the extent of methylprednisolone absorbed following the IV and IM treatment was equivalent in sprite of the greater amount of the hemisuccinate ester reaching the general circulation after IV administration, it appears that the ester is converted in the tissue after IM injection with subsequent absorption as free methylprednisolone.

Distribution: methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. Its apparent volume of distribution is approximately 1.4 L/kg. The plasma protein binding of methylprednisolone in humans is approximately 77%.

Metabolism: in humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. 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.

Excretion: the mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Total clearance is approximately 5 to 6 mL/min/kg.

5.3 Preclinical Safety data

Based on conventional studies of safety pharmacology 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.

Carcinogenesis: long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis: there was no evidence of a potential for genetic and chromosome mutations when tested in limited studies performed in bacteria and mammalian cells.

Reproductive toxicity: corticosteroids have been shown to reduce fertility when administered to rats. 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 Hydroxide

Monosodium Phosphate Dihydrate

6.2 Incompatibilities

The IV compatibility and stability of methylprednisolone sodium succinate solutions and with other drugs in intravenous admixtures is dependent on admixture pH, concentration, time temperature, and the ability of methylprednisolone to solubilize itself. Thus, to avoid compatibility and stability problems, whenever possible it is recommended that methylprednisolone sodium succinate be administered separately from other drugs and as either IV push, through an IV medication chamber, or as an IV piggy-back solution.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Clear glass vial (Type I) closed with gray chlorobutyl rubber stopper and sealed with aluminium/polypropylene flip-off cap contains methylprednisolone (as methylprednisolone sodium succinate) 1 g and 2 g, packed or unpacked in a box of 1, 5, 10 and 12 vials.

6.6 Special precautions for disposal and other handling

Preparation for administration

Methylprednisolone sodium succinate is reconstituted with bacteriostatic water for injection containing 0.9% benzyl alcohol (1g/16 mL vial and 2g/32 mL vial). For IV infusion, the reconstituted methylprednisolone sodium succinate should be further diluted with 5% dextrose, 0.9% sodium chloride, 5% dextrose in 0.9% sodium chloride injection.

Admixture compatibility

This solution may be added to indicated amounts of 5% dextrose in water, isotonic saline solution, or 5% dextrose in isotonic saline solution. Store reconstituted solution below 30^{o} C. Use solution within 48 hours after mixing. Parenteral methylprednisolone sodium succinate should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit.

7. Marketing Authorization Holder

ABLE MEDICAL COMPANY LIMITED

111 Moo. 9 Nong Son, Chiang Yuen,

Mahasarakham 44160, Thailand

8. Marketing Authorization Numbers

xx xxx/xx

9. Date of authorization

DD/MM/YYYY

10. Date of revision of the text

4 June 2020