MEDIXON

Powder for injection

Composition:
Each powder for injection contains methylprednisolone sodium succinate equivalent to methylprednisolone 500 mg.
Each solvent contains bacteriostatic solution with 0.9% of benzyl alcohol as preservative.

Description:
Powder for injection:
Before reconstitution: a white or almost white amorf substances, odorless, and hygroscopic.
After reconstitution: a clear and colorless solution, has a characteristic odor of benzyl alcohol.
Solvent: a clear sterile solution.

Action:
Methylprednisolone is a synthetic corticosteroid with mainly glucocorticoid activity and minimal mineralocorticoid properties. It decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability.

Summary of Pharmacodynamics and Pharmacokinetics:
Methylprednisolone pharmacokinetics is linear, independent of route of administration.
Distribution:
Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. Its apparent volume of distribution is approximately 1.4 l/kg. The plasma protein binding of methylprednisolone in humans is approximately 77%.
Metabolism:
Methylprednisolone is extensively bound to plasma proteins, mainly to globulin and less so to albumin. Only unbound corticosteroid has pharmacological effects or is metabolized. Metabolism occurs in the liver and to a lesser extent in the kidney. In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone.
Metabolism in the liver occurs primarily via the CYP3A4. 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.
Elimination:
Metabolites are excreted in the urine.
The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Total clearance is approximately 5 to 6 ml/minute/kg. Mean elimination half-life ranges from 2.4 to 3.5 hours in normal healthy adults and appears to be independent of the route of administration. **(I p.1; II p.14)**
Total body clearance following intravenous or intramuscular injection of methylprednisolone to healthy adult volunteers is approximately 15–16 l/hour. Peak methylprednisolone plasma levels of 33.67 mcg/100 ml were achieved in 2 hours after a single 40 mg IM injection to 22 adult male volunteers.
No dosing adjustments are necessary in renal failure. Methylprednisolone is hemodialyzable.

Indications:
- Severe hypersensitivity reactions
  - Severe hypersensitivity or allergic reactions not responding to adequate treatment, including: asthma bronchial, contact and atopic dermatitis, serum sickness, allergic rhinitis, drug hypersensitivity reactions, posttransfusion urticaria, acute noninfectious laryngeal edema (adrenaline is drug of first choice).
  - Severe acute and chronic inflammatory and allergic processes involving the eye, such as: herpes zoster ophthalmicus, iritis, iridocyclitis, choroiditis, diffuse posterior uveitis, optic neuritis, sympathetic ophthalmia, anterior segment inflammation, allergic conjunctivitis, allergic corneal marginal ulcers, keratitis. Severe dermatological reactions pemphigus, severe erythema multiforme (Stevens-Johnson syndrome), erythroderma (exfoliative dermatitis), bullous dermatitis herpetiformis, severe form of seborrhea dermatitis, severe psoriasis, myosis fungoides.
- Status asthmaticus.
- Suppression of graft rejection reactions.
- Cerebral edema, including cerebral edema due to primary and metastatic tumors, surgical and radiological treatment following cranial trauma.

- Gastrointestinal diseases
  To tide the patient over a critical period of the disease in: ulcerative colitis, Crohn's disease.
- Fulminating systemic lupus erythematosus.
- Shock unresponsive to conventional therapy of adrenocortical insufficiency. (Hydrocortisone is generally the drug of choice. When mineralocorticoid activity is undesirable, methylprednisolone may be preferred).
- Rheumatic disorders
  For short-term adjuvant treatment in acute phase of the illness or in case of exacerbation in following conditions: post-traumatic osteoarthritis, synovitis of osteoarthritis.
  Rheumatic arthritis, including the juvenile form. In certain instances, low-dose maintenance therapy may be necessary, in which case it is advisable to transfer to oral or depot preparations as appropriate. Acute and subacute bursitis, epicondylitis, acute nonspecific tenosynovitis, acute gouty arthritis, spondylitis ankylopoetica.
- Tuberculosis meningitis (with appropriate antituberculous chemotherapy).

Dosage and Directions for Use:
Methylprednisolone powder for injection may be administered intravenously or intramuscularly, the preferred method for emergency use being intravenous injection given over a suitable time interval. When administering methylprednisolone sodium succinate in high doses intravenously it should be given over a period of at least 30 minutes. Doses up to 250 mg should be given intravenously over a period of at least five minutes.
For intravenous infusion the initially prepared solution may be diluted with 5% dextrose in water, isotonic saline solution, or 5% dextrose in isotonic saline solution. To avoid compatibility problems with other drugs methylprednisolone powder for injection should be administered separately, only in the solutions mentioned.
Undesirable effects may be minimized by using the lowest effective dose for the minimum period.
Parenteral drug products should wherever possible be visually inspected for particulate matter and discoloration prior to administration.

Adults:
Dosage should be varied according to the severity of the condition, initial dosage will vary from 10 to 500 mg. In the treatment of graft rejection reactions following transplantation, a dose of up to 1 gram/day may be required. Although doses and protocols have varied in studies using methylprednisolone sodium succinate in the treatment of graft rejection reactions, the published literature supports the use of doses of this level, with 500 mg to 1 g most commonly used for acute rejection.
Treatment at these doses should be limited to a 48–72-hour period until the patient's condition has stabilized, as prolonged high-dose corticosteroid therapy can cause serious corticosteroid induced side effects.

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

Elderly patients:
Methylprednisolone sodium succinate powder for injection 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 **Precautions/Warnings**).

Detailed recommendations for adults dosage are as follows:
In anaphylactic reactions, adrenaline or noradrenaline should be administered first for an immediate hemodynamic effect, followed by intravenous injection of methylprednisolone sodium succinate with other accepted procedures. There is evidence that corticosteroids through their prolonged hemodynamic effect are of value in preventing recurrent attacks of acute anaphylactic reactions.
In sensitivity reactions, methylprednisolone sodium succinate is capable of providing relief within one-half to two hours. In patients with status asthmaticus, methylprednisolone sodium succinate may be given at a dose of 40 mg intravenously, repeated as dictated by patient response. In some asthmatic patients it may be advantageous to administer by slow intravenous drip over a period of hours.
In graft rejection reactions following transplantation, doses of up to 1 g per day have been used to suppress rejection crisis, with doses of 500 mg to 1 g most commonly used for acute rejection. Treatment should be

continued only until the patient's condition has stabilized usually not beyond 48–72 hours.
In cerebral edema, corticosteroids are used to reduce or prevent the cerebral edema associated with brain tumors (primary or metastatic).
In patients with edema due to tumor, tapering the dose of corticosteroid appears to be important in order to avoid a rebound increase in intracranial pressure. If brain swelling does occur as the dose is reduced (intracranial bleeding having been ruled out), restart larger and more frequent doses parenterally. Patients with certain malignancies may need to remain on oral corticosteroid therapy for months or even life. Similar or higher doses may be helpful to control edema during radiation therapy.

The following are suggested dosage schedules for edemas due to brain tumor.

Schedule A	**Dose (mg)**	**Route**	**Interval in hours**	**Duration**
Preoperative	20	IM	3–6	
During surgery	20 to 40	IV	Hourly	
Postoperative	20	IM	3	24 hours
	16	IM	3	24 hours
	12	IM	3	24 hours
	8	IM	3	24 hours
	4	IM	3	24 hours
	4	IM	6	24 hours
	4	IM	12	24 hours
Schedule B	**Dose (mg)**	**Route**	**Interval in hours**	**Duration**
Preoperative	40	IM	6	2–3
Postoperative	40	IM	6	3–5
	20	Oral	6	1
	12	Oral	6	1
	8	Oral	8	1
	4	Oral	12	1
	4	Oral		1

Aim to discontinue therapy after a total of 10 days.
In the treatment of acute exacerbations of multiple sclerosis in adults, the recommended dose is 1,000 mg daily for 3 days. Methylprednisolone powder for injection 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.

Incompatibility:
Incompabilities:
Incompatible fluids: No information.
Incompatible drugs: Aminophylline, benzylpenicillin, calcium gluconate, ciprofloxacin, cisatracurium, dolasetron, filgrastim, glycopyrrolate, insulin soluble, metaraminol, ondansetron, pantoprazole, potassium chloride, propofol, rocuronium, tigecycline.

Contraindications:
MEDIXON is contraindicated:
– in patients who have systemic fungal infections unless specific anti-infective therapy is employed and in cerebral edema in malaria.
– in patients with known hypersensitivity to methylprednisolone or any component of the formulation.
– for use by the intrathecal route of administration.
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

Precautions/Warnings:
– Immunosuppressant effects/increased susceptibility to infections
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. Suppression of the inflammatory response and immune function

increases the susceptibility to fungal, viral, and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognized.

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

Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed, they should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobin (VZIG) is needed by exposed nonimmune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

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

Similarly, corticosteroids should be used with great care in patients with known or suspected parasitic infections such as *Strongyloides* (threadworm) infestation, which may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal Gram-negative septicemia.

Although MEDIXON is not approved in the UK for use in any shock indication, the following warning statement should be adhered to. Data from a clinical study conducted to establish the efficacy of MEDIXON in septic shock, suggest that a higher mortality occurred in subsets of patients who entered the study with elevated serum creatinine levels or who developed a secondary infection after therapy began. Therefore, this product should not be used in the treatment of septic syndrome or septic shock.

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short course, high-dose corticosteroids did not support their use. However, meta-analysis, and a review suggest that longer courses (5–11 days) of low-dose corticosteroids might reduce mortality.

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

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

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

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

– Blood and lymphatic system

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

– Immune system effects

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

– Endocrine effects

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.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 6 mg methylprednisolone) for greater than 3 weeks, withdrawal should not be abrupt.

Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage. How dose reduction should be carried out depends largely on whether the disease is likely to

relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids, but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 6 mg methylprednisolone is reached, dose reduction should be slower to allow the HPA-axis to recover.

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

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

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

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

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated. **(I p.6; II p.5)**

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

Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease.

There is an enhanced effect of corticosteroids on patients with hypothyroidism. Frequent patient monitoring is necessary in patients with hypothyroidism.

– Metabolism and nutrition

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

– Psychiatric effects

Patients and/or caregivers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting treatment.

Risks may be higher with high doses/systemic exposure, 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/caregivers should be encouraged to seek medical advice if worrying psychological symptoms develop, 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, although such reactions have been reported infrequently.

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

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

– Nervous system effects

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

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

with myasthenia gravis.

– Ocular effects
Frequent patient monitoring is necessary in patients with glaucoma (or a family history of glaucoma) and in patients with ocular herpes simplex, for fear of corneal perforation.
Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

– Cardiac effects
Adverse reactions 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 have been a few reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest associated with the rapid intravenous administration of large doses of MEDIXON (greater than 500 mg administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed and duration of infusion.
Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.
Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss. Frequent patient monitoring is necessary in patients with congestive heart failure or recent myocardial infarction (myocardial rupture has been reported).

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

– 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.
Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.
  - Ulcerative colitis
  - Perforation, abscess, or other pyogenic infections
  - Diverticulitis
  - Fresh intestinal anastomoses
  - Peptic ulceration

– Hepatobiliary effects
High doses of corticosteroids may produce acute pancreatitis.

– Musculoskeletal effects
Particular care is required when considering the use of systemic corticosteroids in patients with myasthenia gravis or osteoporosis (postmenopausal females are particularly at risk) and frequent patient monitoring is necessary.
Osteoporosis is a common but infrequently recognized adverse reactions associated with a long-term use of large doses of glucocorticoid.

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

– Investigations
Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with 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
Corticosteroids should not be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

– Other adverse events

Since complications of treatment with glucocorticoids are dependent on the size of the dose and 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. **(I p.9; II p.8)**
Pheochromocytoma crisis, which may 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:
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.

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

As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.

Drug 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 synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (up regulation) or inhibition of the CYP3A4 enzyme.

- CYP3A4 inhibitors
  Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity. Cotreatment 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.
- CYP3A4 inducers
  Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result.
- CYP3A4 substrates
  In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be inhibited or induced, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration.
- Non-CYP3A4-mediated effects
  Other interactions and effects that occur with methylprednisolone are described in Table 1 below.
  Table 1 provides a list and descriptions of the most common and/or clinically important drug interactions or effects with methylprednisolone.

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

Drug class or type – DRUG or SUBSTANCE	Interaction	Effect
Macrolide antibacterial – Troleandomycin	CYP3A4 inhibitor	CYP3A4 inhibitor An increase in the plasma concentration of methylprednisolone

Antibacterial – Isoniazid – Grapefruit juice		may occur. The dose of methylprednisolone may need to be titrated to avoid steroid toxicity. In addition, there is a potential effect of methylprednisolone on the acetylation rate and clearance of isoniazid.
Antibiotic, antitubercular – Rifampin Anticonvulsants – Phenobarbital – Phenytoin	CYP3A4 inducer	CYP3A4 inducer A decrease in the plasma concentration of methylprednisolone may occur. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result.
Antiemetic – Aprepitant – Fosaprepitant Antifungal – Itraconazole – Ketoconazole Antivirals – HIV-protease inhibitors Calcium channel blocker – Diltiazem Contraceptives (oral) – Ethinylestradiol/norethisteron e	CYP3A4 inhibitor (and substrate)	CYP3A4 inhibitor (and substrate) The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with administration. Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.
Immunosuppressant – Ciclosporin Macrolide antibacterial – Clarithromycin – Erythromycin		Ciclosporin 1) Mutual inhibition of metabolism occurs with concurrent use of ciclosporin and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon coadministration. 2) Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin.
Anticonvulsants – Carbamazepine	CYP3A4 inducer (and substrate)	CYP3A4 inducer (and substrate) The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with administration.
Immunosuppressant – Cyclophosphamide – Tacrolimus	CYP3A4 substrate	CYP3A4 substrate The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with administration.
Anticoagulants (oral)	Non-CYP3A4-mediated effects	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticholinergics – Neuromuscular blockers		Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (see **Precautions/Warnings**, Musculoskeletal effects, for additional information.) 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
Antidiabetics		Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Aromatase inhibitors – Aminoglutethimide		Aminoglutethimide-induced adrenal suppression may impede endocrine changes caused by prolonged glucocorticoid treatment.

NSAIDs (nonsteroidal anti-inflammatory drugs) – high-dose aspirin (acetylsalicylic acid)		1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Methylprednisolone may increase the clearance of high-dose aspirin. This decrease in salicylate serum levels could lead to an increased risk of salicylate toxicity when methylprednisolone is withdrawn.
Potassium depleting agents – Diuretics – Amphotericin B – Beta2 agonists – Xanthenes		When corticosteroids are administered concomitantly with potassium depleting agents, patients should be observed closely for development of hypokalemia. Corticosteroids antagonize the diuretic effect of diuretics.

Corticosteroids antagonize the hypotensive effect of all antihypertensives. There is an increased risk of hypokalemia when corticosteroids are given with cardiac glycosides.
The effects of corticosteroids may be reduced for 3–4 days after mifepristone.

Use in Pregnancy and Lactation:

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

– Pregnancy
The ability of corticosteroids to cross the placenta varies between individual drugs, however, methylprednisolone does cross the placenta.
Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate, intrauterine growth retardation, and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate in man, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intrauterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the nongravid state.
Cataracts have been observed in infants born to mothers undergoing long-term treatment with corticosteroids during pregnancy.

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

Adverse Reactions:

Under normal circumstances, MEDIXON therapy would be considered as short-term. However, the possibility of adverse reactions attributable to corticosteroid therapy should be recognized, particularly when high-dose therapy is being used. Such adverse reactions include:

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Common	Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs).
	Not known	Opportunistic infection. Recurrence of dormant tuberculosis.
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Not known	Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.
Blood and lymphatic system disorders	Not known	Leukocytosis.
Immune system disorders	Not known	Drug hypersensitivity (including anaphylactic reaction and anaphylactoid reaction with or without circulatory collapse, cardiac arrest, bronchospasm).
Endocrine disorders	Common	Cushingoid
	Not known	Hypopituitarism (including suppression of the hypothalamo-

		pituitary-adrenal axis), steroid withdrawal syndrome (including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules, and loss of weight).
Metabolism and nutrition disorders	Common	Sodium retention; fluid retention.
	Not known	Glucose tolerance impaired; alkalosis hypokalemic; dyslipidemia; increased requirements for insulin (or oral hypoglycemic agents in diabetics); negative nitrogen balance (due to protein catabolism); blood urea increased; increased appetite (which may result in weight increased); lipomatosis.
Psychiatric disorders	Common	A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, psychological dependence and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioral disturbances, irritability, anxiety, sleep disturbances, 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; the frequency is unknown.
Nervous system disorders	Not known	Increased intracranial pressure with papilledema [benign intracranial hypertension]; convulsion; amnesia; cognitive disorder; dizziness; headache.
Eye disorders	Common	Posterior subcapsular cataracts.
	Not known	Exophthalmos; glaucoma; papilledema with possible damage to the optic nerve; corneal or scleral thinning; exacerbation of ophthalmic viral or fungal disease.
Ear and labyrinth disorders	Not known	Vertigo.
Cardiac disorders	Not known	Congestive heart failure in susceptible patients; arrhythmia.
Vascular disorders	Common	Hypertension.
	Not known	Hypotension; thromboembolism.
Respiratory, thoracic, and mediastinal disorders	Not known	Hiccups.
Gastrointestinal disorders	Common	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer hemorrhage)
	Not known	Gastric hemorrhage; intestinal perforation; pancreatitis; peritonitis; ulcerative esophagitis; esophagitis; esophageal candidiasis; abdominal pain; abdominal distension; diarrhea; dyspepsia; nausea; vomiting; bad taste in mouth may occur especially with rapid administration.
Skin and subcutaneous tissue disorders	Common	Peripheral edema; ecchymosis; skin atrophy (thin fragile skin); acne.
	Not known	Angioedema; petechiae; skin striae; telangiectasia; skin hypopigmentation or hyperpigmentation; hirsutism; rash; erythema; pruritus; urticaria; hyperhidrosis.
Musculoskeletal and connective tissue disorders	Common	Growth retardation (in children); osteoporosis; muscular weakness.
	Not known	Osteonecrosis; pathological fracture; muscle atrophy; myopathy; neuropathic arthropathy; arthralgia; myalgia.
Reproductive system and breast disorders	Not known	Irregular menstruation; amenorrhea.
General disorders and administration site conditions	Common	Impaired wound healing.
	Not known	Injection site reaction; fatigue; malaise; withdrawal symptoms - too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension, and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given.
Investigations	Common	Blood potassium decreased (potassium loss).
	Not known	Alanine aminotransferase increased (ALT, SGPT); aspartate aminotransferase increased (AST, SGOT); blood alkaline phosphatase increased; intraocular pressure increased; carbohydrate tolerance decreased; urine calcium increased; suppression of reactions to skin tests.
Injury, poisoning, and procedural	Not known	Tendon rupture (particularly of the achilles tendon); spinal

complications		compression fracture (vertebral compression fractures).

Common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (frequency cannot be estimated).

Overdosage, Symptoms, and Treatment:
There is no clinical syndrome of acute overdosage with methylprednisolone powder for injection. Methylprednisolone is dialyzable. Following chronic overdosage the possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. In such event the patient may require to be supported during any further stressful episode.

Presentation:
1 box contains 1 vial of methylprednisolone sodium succinate equivalent to methylprednisolone 500 mg and 1 ampoule of solvent 8 ml.

Storage Conditions:
Powder for injection:
Before and after reconstitution: Protect from light and store at temperatures below 30°C.
Solvent: Protect from light and store at temperatures below 30°C.

Shelf-life:
Powder for injection:
The injections can be used within 24 months from the date of manufacturer if kept as recommended. Should be use immediately after prepared. For single use only. Discard any unused portion.
Solvent: The solvent can be used within 36 months from the date of manufacturer if kept as recommended.

KEEP MEDICINES OUT OF REACH OF CHILDREN.

ON MEDICAL PRESCRIPTION ONLY.

Registration Number:
MEDIXON Powder for injection 500 MG-MAL16095025ACZ

Manufactured by:
PT Bernofarm
Jl. Gatot Subroto No. 68,
Sidoarjo 61252
Indonesia

For:
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia

Product registration holder:
Averroes Pharmaceuticals Sdn. Bhd.
03-08-01 & 03-09-01, Block 3
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