

DEXAMETHASONE MYLAN INJECTION



Dexamethasone sodium phosphate

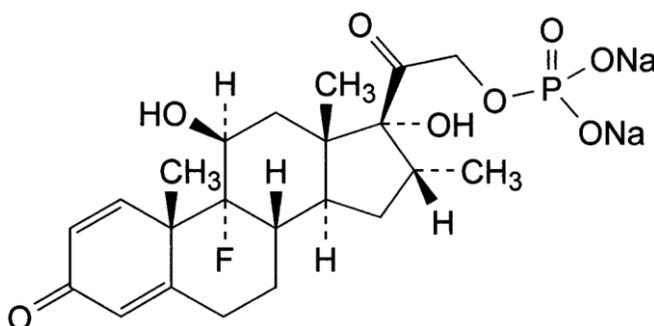
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient : Dexamethasone sodium phosphate

Chemical name : 9-fluoro-11 β ,17-dihydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-yl disodium phosphate

Structural formula :



Molecular formula : C₂₂H₂₈FN₂O₈P

Molecular weight : 516.4

CAS Registry no. : 2392-39-4

DESCRIPTION

Dexamethasone sodium phosphate is a white or slightly yellow, very hygroscopic, crystalline powder. It is odourless or has a slight odour of alcohol. Dexamethasone sodium phosphate is freely soluble in water, slightly soluble in alcohol, practically insoluble in chloroform and ether and very slightly soluble in 1,4-dioxane.

DEXAMETHASONE MYLAN INJECTION contains dexamethasone sodium phosphate 4.4 mg/mL (equivalent to 4 mg dexamethasone phosphate) as the active ingredient. The excipients are sodium citrate anhydrous and creatinine, pH of a 1% solution in water is between 7.5 and 9.5.

PHARMACOLOGY

Dexamethasone is a synthetic adrenocorticosteroid with glucocorticoid activity. It is one of the most active glucocorticoids, being about 25 to 30 times as potent as hydrocortisone. Unlike hydrocortisone, dexamethasone has little if any mineralocorticoid activity.

Dexamethasone has anti-inflammatory and immunosuppressant activity. Glucocorticoids prevent the development of the inflammatory response, i.e. redness, swelling, tenderness. They also inhibit capillary dilation and phagocytosis and appear to prevent the hypersensitivity responses which occur after antigen/ antibody reactions.

The principal metabolic actions of dexamethasone are on gluconeogenesis, glycogen deposition and protein and calcium metabolism. Dexamethasone also influences the mobilisation, oxidation, synthesis and storage of fats.

Dexamethasone suppresses the release of adrenocorticotrophic hormone (ACTH) from the pituitary, resulting in inhibition of endogenous corticotrophin secretion.

Except for its use in the treatment of adrenal insufficiency, dexamethasone does not cure disease. Rather, the anti-inflammatory and immunosuppressant actions of dexamethasone suppress the symptoms associated with the disease.

PHARMACOKINETICS

Dexamethasone sodium phosphate is absorbed rapidly following intramuscular or intravenous injection.

Intramuscular injections of dexamethasone phosphate give maximum plasma concentrations of dexamethasone at one hour. The biological half-life of dexamethasone is about 190 minutes.

In the circulation, small amounts of dexamethasone are bound to plasma proteins. Synthetic corticosteroids such as dexamethasone are less extensively protein bound and more slowly metabolised than hydrocortisone. Dexamethasone penetrates into tissue fluids and cerebrospinal fluids. Metabolism occurs in most tissues, but primarily in the liver. The inactive metabolites are excreted in the urine, mainly as glucuronides and sulfates but also as unconjugated metabolites. Small amounts of unchanged drug are also excreted in the urine. Up to 65% of a dose of dexamethasone is excreted in the urine within 24 hours.

INDICATIONS

Replacement therapy

Adrenocortical insufficiency

Dexamethasone has predominantly glucocorticoid activity and, therefore, is not a complete replacement therapy in cases of adrenocortical insufficiency. Dexamethasone should be supplemented with salt and/or a mineralocorticoid, such as deoxycorticosterone. When so supplemented, dexamethasone is indicated in the following:

- Acute adrenocortical insufficiency.
- Addison's disease,
- Bilateral adrenalectomy.
- Relative adrenocortical insufficiency.
- Primary and secondary adrenocortical insufficiency.

Prolonged administration of adrenocortical steroids can produce dormancy of the adrenal cortex. The reduced secretory capacity gives rise to a state of relative adrenocortical insufficiency which persists for a varying length of time after therapy is discontinued. Should a patient be subjected to sudden stress during this period of reduced secretion (for up to two years after therapy has ceased) the steroid output may not be adequate. Steroid therapy should, therefore, be reinstated to help cope with stress such as that associated with surgery, trauma, burns or severe infections where specific antibiotic therapy is available.

Disease therapy

Dexamethasone is indicated for the therapy of the following diseases:

1. *Collagen diseases.* Systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, giant cell arteritis, adjunctive therapy for short-term administration during an acute episode or exacerbation, acute rheumatic carditis during an exacerbation or as maintenance therapy.
2. *Pulmonary disorders.* Status asthmaticus, chronic asthma, sarcoidosis, respiratory insufficiency.
3. *Blood disorders.* Leukaemia, idiopathic thrombocytopenic purpura in adults, acquired (autoimmune) haemolytic anaemia.
4. *Rheumatic diseases.* Rheumatoid arthritis, osteoarthritis, adjunctive therapy for short-term administration during an acute episode or exacerbation of rheumatoid arthritis or osteoarthritis.
5. *Skin diseases.* Psoriasis, erythema multiforme, pemphigus, neutrophilic dermatitis, localised neurodermatitis, exfoliative dermatitis, sarcoidosis of skin, severe seborrhoeic dermatitis, contact dermatitis.
6. *Gastrointestinal disorders.* Ulcerative colitis, regional enteritis.
7. *Oedema.* Cerebral oedema associated with primary or metastatic brain tumours, neurosurgery or stroke, oedema associated with acute noninfectious laryngospasm (or laryngitis).
8. *Eye disorders.* Allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy.
9. *Neoplastic states.* Cerebral neoplasms, hypercalcaemia associated with cancer, leukaemias and lymphomas in adults, acute leukaemia in children.
10. *Endocrine disorders.* Adrenal insufficiency.

Preoperative and postoperative support

Dexamethasone may be used in any surgical procedure when the adrenocortical reserve is doubtful. This includes the treatment of shock due to excessive blood loss during surgery.

Shock

Dexamethasone may be used as an adjunct in the treatment of shock. Refer to **DOSAGE AND ADMINISTRATION**. Dexamethasone should not be used as a substitute for normal shock therapy.

CONTRAINDICATIONS

Systemic fungal infections (see **PRECAUTIONS**). Hypersensitivity to dexamethasone or other corticosteroids or to any component of the injection. Administration of live virus vaccines (see **PRECAUTIONS**). In patients with myasthenia gravis, peptic ulcer, osteoporosis or psychoses.

PRECAUTIONS

Corticosteroids may increase susceptibility to or mask the symptoms of infection, and therefore should be used with caution in patients with systemic infections. Chickenpox, measles and other infections can have a more serious or even fatal effect in non-immune children or adults on corticosteroids. Immunosuppression is most

likely to occur in patients receiving longer term, high dose systemic corticosteroid treatment, however, patients receiving moderate doses for short periods, or low doses over a prolonged period, may also be at risk.

Corticosteroids should be administered with caution to patients with latent tuberculosis or tuberculin reactivity, as reactivation of the disease may occur. These patients should, therefore, undergo chemoprophylaxis during prolonged corticosteroid therapy.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Administration of live virus vaccines is contraindicated in individuals receiving immunosuppressive doses of corticosteroids (see **CONTRAINDICATIONS**). If inactivated viral or bacterial vaccines are administered to patients receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunisation procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g. for Addison's disease.

Long-term treatment should not be abruptly discontinued, as too rapid withdrawal may lead to drug induced secondary adrenocortical insufficiency. This may be minimised by gradual dosage reduction. This type of relative insufficiency may persist for months after therapy is discontinued. Therefore, in any situation of stress occurring in that period (such as anaesthesia, surgery or trauma) corticosteroid doses may need to be increased or the therapy reinstated. Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia and malaise.

Dexamethasone should be used only with extreme caution in patients with diabetes mellitus, infectious diseases, congestive heart failure, chronic renal failure, diverticulitis, hypertension, keratitis, epilepsy, nonspecific ulcerative colitis (if there is a probability of impending perforation, abscess or other pyogenic infection), fresh intestinal anastomoses, active or latent peptic ulcer, osteoporosis, myasthenia gravis or in elderly persons.

Geriatric patients may be more likely to develop hypertension and osteoporosis as a result of corticosteroid therapy.

Corticosteroids should be used with caution in patients who have had a recent cardiac infarction, as there have been reports of an apparent association between the use of corticosteroids and left ventricular free wall rupture in these patients.

Corticosteroids show an enhanced effect in patients with hypothyroidism or cirrhosis.

Intra-articular injection of corticosteroids may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Local injection of a steroid into an infected site is to be avoided. Corticosteroids should not be injected into unstable joints.

Frequent intra-articular injection may result in damage to joint tissues. Patients should be advised strongly of the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

Carcinogenesis, mutagenesis, impairment of fertility

No information is available on the carcinogenicity or mutagenicity of dexamethasone. Corticosteroids may increase or decrease the motility and number of spermatozoa in some patients.

Use in pregnancy (Category C)

In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations). These findings do not seem to be relevant to humans. Reduced placental and birthweight have been recorded in animals and humans after long-term treatment. Since the possibility of suppression of the

adrenal cortex in the newborn baby after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the fetus when prescribing corticosteroids. However, the short-term use of antepartum corticosteroids for the prevention of respiratory distress syndrome, when warranted, does not seem to pose a risk.

Australian categorisation definition of Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Use in lactation

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production or cause other unwanted effects in breastfed infants. Women taking corticosteroids should be advised not to breastfeed.

Laboratory tests

Dexamethasone suppression tests may be affected by drugs which enhance the metabolic clearance of corticosteroids (see **INTERACTIONS WITH OTHER MEDICINES**).

False negative results in the dexamethasone suppression test have been reported in patients being treated with indomethacin or high doses of benzodiazepines or cyproheptadine.

Corticosteroids have been reported to alter the response to anticoagulant agents (see **INTERACTIONS WITH OTHER MEDICINES**). The prothrombin time should be checked frequently in patients receiving these combinations.

Corticosteroids may affect a wide range of diagnostic tests. They may affect brain and skeletal imaging using ^{99}Tc , by decreasing uptake of ^{99}Tc into cerebral tumours or bone, respectively, and may decrease ^{123}I and ^{131}I uptake into the thyroid. Corticosteroids may alter the results of the gonadorelin test for hypothalamic pituitary gonadal axis function, affect thyroid function test results, and suppress skin test reactions including tuberculin and histoplasmin skin tests and patch tests for allergy. Corticosteroids may also affect the nitroblue tetrazolium test for bacterial infection and produce false negative results.

INTERACTIONS WITH OTHER MEDICINES

Concurrent administration of hepatic enzyme inducing agents, including barbiturates, phenylbutazone, phenytoin or rifampicin may increase the metabolism and thus reduce the effects of corticosteroids.

Ephedrine and aminoglutethimide may also increase dexamethasone metabolism.

Antithyroid agents, oestrogens and other oral contraceptives may decrease hepatic metabolism and thus increase the effects of corticosteroids.

The effects of anticoagulant agents are usually decreased (but may be increased in some patients) if corticosteroids are administered concurrently.

Seizures have reportedly occurred in adult and paediatric patients receiving high dose corticosteroid therapy concurrently with cyclosporin.

Concurrent administration of dexamethasone with anticoagulants, heparin, streptokinase, urokinase, alcohol or nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin may increase the risk of gastrointestinal ulceration or haemorrhage.

Potassium loss may occur as a result of dexamethasone administration (see **ADVERSE EFFECTS**). Concurrent administration of corticosteroids with potassium depleting diuretics (such as thiazides, frusemide or ethacrynic acid), carbonic anhydrase inhibitors or amphotericin may result in severe hypokalaemia.

The activity of digitalis glycosides and nondepolarising neuromuscular blocking agents may be potentiated as a result of glucocorticoid induced hypokalaemia.

The efficacy of potassium supplements and potassium sparing diuretics on serum potassium concentrations may be reduced by concurrent corticosteroid administration. Monitoring of serum potassium concentration is, therefore, recommended.

Glucocorticoids may increase blood glucose concentrations. Dosage adjustment of asparaginase and of antidiabetic agents such as sulfonylureas and insulins may be necessary.

ADVERSE EFFECTS

The following adverse reactions have been reported with dexamethasone therapy. Except for allergic reactions, the adverse effects listed have been associated with prolonged therapy and/or high doses.

Endocrine effects

Adrenal suppression, menstrual irregularities, development of Cushingoid state, secondary adrenocortical and pituitary unresponsiveness particularly in times of stress (e.g. trauma, surgery or illness), decreased carbohydrate tolerance, increased requirements for insulin or oral hypoglycaemic agents in diabetes, development of diabetes mellitus, hyperglycaemia, hirsutism, growth suppression in children.

Cardiovascular effects

Thromboembolism, polymorphonuclear leucocytosis, neuropathy, vasculitis, impaired myocardial contractility (prolonged treatment), congestive heart failure in susceptible patients, myocardial rupture following recent cardiac infarction, hypertrophic cardiomyopathy in low birthweight infants.

Musculoskeletal effects

Osteoporosis, arthropathy, muscular atrophy, muscle weakness, steroid myopathy, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture. These may occur as a result of protein catabolism associated with prolonged glucocorticoid therapy.

Ocular effects

Increased intraocular pressure, glaucoma, cataracts, exophthalmos, retinopathy of prematurity, enhanced establishment of secondary fungal and viral eye infections.

Dermatological effects

Impaired wound healing, allergic dermatitis, urticaria, erythema, thin fragile skin, petechiae and ecchymoses, increased sweating, may suppress skin test reactions, burning or tingling especially in the perineal area (after intravenous injection), angioneurotic oedema, acne, striae, easy bruising.

Gastrointestinal effects

Peptic ulcer with possible perforation and haemorrhage, pancreatitis, perforation of the small or large bowel particularly in patients with inflammatory bowel disease, abdominal distension, ulcerative oesophagitis, nausea.

Neurological effects

Euphoric side effects, mental disturbances, headache, convulsions, increased intracranial pressure with papilloedema, vertigo.

Fluid and electrolyte disturbances

Electrolyte imbalance (retention of sodium and water with oedema and hypertension), potassium loss, hypokalaemic alkalosis, hypocalcaemia.

Metabolic effects

Nitrogen depletion, negative nitrogen balance due to protein catabolism.

Other effects

Allergic reactions, anaphylactic or hypersensitivity reactions, weight gain, increased appetite, malaise, hiccups.

Glucocorticoids, especially in large doses, increase susceptibility to infection and may mask the symptoms of infection (see **PRECAUTIONS**).

A steroid withdrawal syndrome, seemingly unrelated to adrenocortical insufficiency and consisting of anorexia, nausea and vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss and/or hypotension, has been reported following abrupt withdrawal of glucocorticoids.

Hyperpigmentation or hypopigmentation, subcutaneous and cutaneous atrophy, sterile abscess, postinjection flare (following intra-articular use) and Charcot-like arthropathy have also been associated with parenteral corticosteroid therapy.

DOSAGE AND ADMINISTRATION

DEXAMETHASONE MYLAN INJECTION may be administered intravenously or intramuscularly for systemic effect, or as an intrasynovial or soft tissue injection for local effect.

Dosage of dexamethasone sodium phosphate is usually expressed in terms of dexamethasone phosphate.

For single patient use. Use once only and discard any residue.

Intravenous and intramuscular administration

Dosage requirements are variable and must be individualised on the basis of the disease being treated and patient response. Intravenous or intramuscular dosage usually ranges from 0.5 to 24 mg of dexamethasone phosphate daily. The duration of therapy is dependent on the clinical response of the patient and as soon as improvement is indicated, the dosage should be adjusted to the minimum required to maintain the desired clinical response. Withdrawal of the drug on completion of therapy should be gradual.

Parenteral dexamethasone is generally reserved for patients who are unable to take the drug orally or for use in an emergency situation.

Shock (of haemorrhagic, traumatic or surgical origin).

The usual dose for the treatment of shock is 2 to 6 mg/kg bodyweight as a single intravenous injection. This may be repeated in two to six hours if shock persists.

An alternative regimen of 20 mg by intravenous injection initially, followed by continuous intravenous infusion of 3 mg/kg bodyweight per 24 hours, has been suggested. If required for intravenous infusion,

DEXAMETHASONE MYLAN INJECTION may be diluted with glucose or sodium chloride injection. High dose therapy should be continued only until the patient's condition has stabilised and usually for no longer than 48 to 72 hours.

To avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the mixture and, if storage is necessary, store solution at 2 to 8°C. Infusion should be completed within 24 hours of preparation of the solution and any residue discarded.

Warning

Further diluted solutions which are not clear or which show evidence of particulate matter contamination should be discarded.

Cerebral oedema

The treatment schedule and route of administration should reflect the severity and aetiology of the cerebral oedema. Treatment needs to be tailored to the individual response. An initial dose of 10 mg intravenously followed by 4 mg intramuscularly every six hours until the symptoms of oedema subside (usually after 12 to 24 hours). After two to four days the dosage should be reduced and gradually stopped over a period of five to seven days. Patients with cerebral malignancy may require maintenance therapy with doses of 2 mg intramuscularly or intravenously two to three times daily.

High doses of dexamethasone may be used to initiate short-term intensive therapy for acute cerebral oedema. Following an initial high loading dose, the dose is scaled down over the seven to ten day period of intensive therapy and subsequently reduced to zero over the next seven to ten days. (See Table 1 for high dose schedule.)

DEXAMETHASONE MYLAN INJECTION dexamethasone sodium phosphate injection

Table 1: High Dose Schedule

Day	Adults	Children >35 kg	Children <35 kg
Initial dose	50 mg IV	25 mg IV	20 mg IV
1 st day	8 mg IV every 2 hrs	4 mg IV every 2 hrs	4 mg IV every 3 hrs
2 nd day	8 mg IV every 2 hrs	4 mg IV every 2 hrs	4 mg IV every 3 hrs
3 rd day	8 mg IV every 2 hrs	4 mg IV every 2 hrs	4 mg IV every 3 hrs
4 th day	4 mg IV every 2 hrs	4 mg IV every 4 hrs	4 mg IV every 6 hrs
5 th – 8 th day	4 mg IV every 4 hrs	4 mg IV every 6 hrs	2 mg IV every 6 hrs
After 8 days	Decrease by daily reduction of 4 mg	Decrease by daily reduction of 2 mg	Decrease by daily reduction of 1 mg

Note: The intravenous and intramuscular routes of administration of dexamethasone injection should only be used where acute illness or life-threatening conditions exist. Oral therapy should be substituted as soon as possible.

Intrasynovial and soft tissue injections.

Dosage varies with the degree of inflammation and the size and location of the affected area. Injections may be repeated from once every three to five days (e.g. for bursae) to once every two to three weeks (for joints). Frequent intra-articular injection may result in damage to joint tissues. (See Table 2 for dosages.)

DEXAMETHASONE MYLAN INJECTION dexamethasone sodium phosphate injection

Table 2: Intrasynovial and soft tissue injection

Site of Injection	Dosage
Large joints	2 mg to 4 mg
Small joints	800 microgram to 1 mg
Bursae	2 mg to 3 mg
Tendon sheaths	400 microgram to 1 mg

Soft tissue infiltration	2 mg to 6 mg
Ganglia	1 mg to 2 mg

OVERDOSAGE

Symptoms

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. Exaggeration of corticosteroid related adverse effects may occur including hypertension, oedema, peptic ulceration, hyperglycaemia and altered mental state. Anaphylactic or hypersensitivity reactions may occur.

Treatment

No antidote is available. Treatment of overdosage is symptomatic. The dosage should be reduced or the drug withdrawn. Anaphylactic and hypersensitivity reactions may be treated with adrenaline (epinephrine), positive pressure artificial respiration and aminophylline. The patient should be kept warm and quiet.

In case of overdose, immediately contact the Poisons Information Centre for advice (In Australia, call 13 11 26. In New Zealand, call 0800 764 766).

PRESENTATION AND STORAGE CONDITIONS

Solution for injection (clear, colourless solution, free from visible particulate matter).

Glass vials:

4 mg/ mL

8 mg/2 mL

Available in packs of 5's and 10's.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF
THERAPEUTIC GOODS (THE ARTG)**

02/03/2011

DATE OF MOST RECENT AMENDMENT:

18/05/2015

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