1.3.1.3. Leaflet

DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP

Presentation

A clear, colourless solution containing in each mL 4.37 mg Dexamethasone Sodium Phosphate USP equivalent to 4.0 mg dexamethasone phosphate or approximately 3.33 mg dexamethasone.

Excipients: Creatinine 8.0 mg/mL, Sodium Citrate 10.0 mg/mL, Sodium methyl parahydroxybenzoate 0.9 mg/mL, Sodium propyl parahydroxybenzoate 0.1 mg/mL, Sodium Hydroxide and Citric Acid monohydrate to adjust pH, Water for Injections.

Excipient with known effects: sodium

Uses

Corticosteroid.
For use in certain endocrine and non-endocrine disorders responsive to corticosteroid therapy.

Systemic administration: DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP is recommended for systemic administration by intravenous or intramuscular injection when oral therapy is not feasible or desirable in the following conditions.

Endocrine disorders: Primary or secondary adrenocortical insufficiency: (hydrocortisone or cortisone is the first choice, but synthetic analogues may be used with mineralocorticoids where applicable and, in infancy, mineralocorticoid supplementation is particularly important.)

Non-endocrine disorders: DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP may be used in the treatment of non-endocrine corticosteroid responsive conditions including:

Allergy and anaphylaxis: Angioneurotic oedema and anaphylaxis.

Gastro-intestinal: Crohn's disease and ulcerative colitis.

Infection (with appropriate chemotherapy): Miliary tuberculosis and endotoxic shock.

Neurological disorders: Raised intracranial pressure secondary to cerebral tumours and infantile spasms.

Respiratory: Bronchial asthma and aspiration pneumonitis.

Skin disorders: Toxic epidermal necrolysis.

Shock: Adjunctive treatment where high pharmacological doses are needed. Treatment is an adjunct to, and not a substitute for specific and supportive measures the patient may require. Dexamethasone has been shown to be beneficial when used in the early treatment of shock, but it may not influence overall survival.

Local administration: DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP is suitable for intra-articular or soft-tissue injection as adjunctive therapy for short-term administration in:

- *Soft-tissue disorders* such as carpal tunnel syndrome and tenosynovitis.
- *Intra-articular disorders* such as rheumatoid arthritis and osteoarthritis with an inflammatory component. DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP may be injected intralesionally in selected skin disorders such as cystic acne vulgaris, localised lichen simplex, and keloids.

Dosage and administration

DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP can be given without mixing or dilution. Use only clear and colourless solutions. Discard any unused solution after opening ampoule. Use the contents of the injection solution only once.

All dosage recommendations are given in units of dexamethasone phosphate.

Intravenous and intramuscular injection:
General considerations

Dosage must be individualized on the basis of the disease and the response of the patient. In order to minimize side effects, the lowest possible dosage adequate to control the disease process should be used (see 'Side Effects').

Usually the parenteral dosage ranges are one-third to one-half the oral dose, given every 12 hours.

The usual initial dosage is 0.5 - 20 mg (0.125 - 5 mL) a day. In situations of less severity, lower doses will generally suffice. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified. In these circumstances, the slower rate of absorption by intramuscular administration should be recognised.

The initial dosage should be maintained or adjusted until a satisfactory response is noted. Both the dose in the evening, which is useful in alleviating morning stiffness, and the divided dosage regimen are associated with greater suppression of the hypothalamo-pituitary-adrenal axis.

After a favourable response is noted, the proper maintenance dosage should be determined by decreasing the initial dosage by small amounts at appropriate intervals to the lowest dosage which will maintain an adequate clinical response. Chronic dosage should preferably not exceed 500 micrograms dexamethasone daily.

Close monitoring of drug dosage is needed.

If DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP is to be stopped after it has been given for more than a few days, it should be withdrawn gradually rather than stopped abruptly.

Whenever possible, the intravenous route should be used for the initial dose and for as many subsequent doses as are given while the patient is in shock (because of the irregular rate of absorption of any medicament administered by any other route in such patients).When the blood pressure responds, use the intramuscular route until oral therapy can be substituted. For the comfort of the patient, not more than 2 ml should be injected intramuscularly at any one site.

Emergencies treatment

The usual dose of DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP by intravenous or intramuscular injection is 4 - 20 mg (1 - 5 mL), depending on the severity of the condition (see also «Shock»).

This dose may be repeated until adequate response is noted. After initial improvement, single doses of 2 - 4 mg (0.5 - 1 mL) repeated as necessary, should be sufficient. The total daily dosage usually need not exceed 80 mg (20 mL), even in severe conditions.

When constant maximal effect is desired, dosage must be repeated at three-hour or four-hour intervals, or maintained by slow intravenous drip. Intravenous and intramuscular injections are advised in acute illness. When the acute stage has passed, oral steroid therapy should be substituted as soon as feasible.

Shock (of haemorrhagic, traumatic or surgical)

Usually 2 to 6 mg/kg body weight as a single intravenous injection. This may be repeated in two to six hours if shock persists. Alternatively, this may be followed immediately by the same dose in an intravenous infusion. Therapy with DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP is an adjunct to, and not a replacement for conventional therapy. Administration of these high doses should be continued only until the patient's condition has stabilised and usually no longer than 48 - 72 hours.

Cerebral oedema

Associated with primary or metastatic brain tumour, pre-operative preparation of patients with increased intracranial pressure secondary to brain tumour: initially 10 mg (2.5 mL) intravenously, followed by 4 mg (1 mL) intramuscularly every six hours until symptoms of cerebral oedema subside. Response is usually noted within 12 - 24 hours; dosage may be reduced after two to four days and gradually discontinued over five to seven days.
High doses of DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP are recommended for initiating short-term intensive therapy for acute life-threatening cerebral oedema. Following the high loading dose schedule of the first day of therapy, 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. When maintenance therapy is required, substitute oral Dexamethasone as soon as possible (see table below).

Palliative management of recurrent or inoperable brain tumours: Maintenance therapy should be determined for each patient: 2 mg (0.5 mL) two or three times a day may be effective. The smallest dosage necessary to control cerebral oedema should be used. Suggested high dose schedule in cerebral oedema:

Adults:

Initial Dose	50 mg IV
1st day	8 mg IV every 2 hours
2nd day	8 mg IV every 2 hours
3rd day	8 mg IV every 2 hours
4th day	4 mg IV every 2 hours
5th day - 8th day	4 mg IV every 4 hours
Thereafter	decrease by daily reduction of 4 mg

Children (35 kg and over):

Initial Dose	25 mg IV
1st day	4 mg IV every 2 hours
2nd day	4 mg IV every 2 hours
3rd day	4 mg IV every 2 hours
4th day	4 mg IV every 4 hours
5th day - 8th day	4 mg IV every 6 hours

Thereafter	decrease by daily reduction of 2 mg

Children (below 35 kg):

Initial Dose	20 mg IV
1st day	4 mg IV every 3 hours
2nd day	4 mg IV every 3 hours
3rd day	4 mg IV every 3 hours
4th day	4 mg IV every 6 hours
5th day - 8th day	2 mg IV every 6 hours
Thereafter	decrease by daily reduction of 1 mg

Intrasynovial, intralesional, and soft-tissue injection

In general, these injections are employed when only one or two joints or areas are affected.

Some of the usual single doses are:

Site of injection	Amount of dexamethasone phosphate
Large joints (e.g. knee)	2 - 4 mg (0.5 - 1 mL)
Small joints (e.g. interphalangeal, temporomandibular)	0.8 - 1 mg (0.2 - 0.25 mL)
Bursae	2 - 3 mg (0.5 - 0 .75 mL)
Tendon sheaths*	0.4 - 1 mg (0.1 - 0.25 mL)
Soft-tissue infiltration	2 - 6 mg (0.5 - 1.5 mL)
Ganglia	1 - 2 mg (0.25 - 0.5 mL)

* Injection should be made into the tendon sheath, and not directly into the tendon.

Frequency of injection: once every three to five days to once every two to three weeks, depending on response.

Use in children

Dosage should be limited to a single dose on alternate days to minimise suppression of the hypothalamo-pituitary-adrenal axis.

Use in the elderly

Treatment of elderly patients, particularly if long term, should be planned bearing in mind the more serious consequences of the common side effects of corticosteroids in old age, especially osteoporosis, diabetes, hypertension, susceptibility to infection and thinning of the skin.

Close clinical supervision is required to avoid life-threatening reactions (see 'Side-effects').

Contra-indications

Systemic fungal infection; systemic infection unless specific anti-infective therapy is given; hypersensitivity to any component of this medication.

Administration of live virus vaccines (see 'Precautions').

Warnings and Precautions for use

Warnings: Frequent intra-articular injections over a prolonged period may lead to joint destruction with bone necrosis. Intra-articular injection of corticosteroid may produce systemic adverse reactions including adrenal suppression.

Precautions: Undesirable effects may be minimised by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity. Where reduction in dosage is possible, the reduction should be gradual (see 'Dosage and administration').

Corticosteroids may exacerbate systemic fungal infections and, therefore, should not be used in the presence of such infections unless they are needed to control drug reactions due to amphotericin. Moreover, there have been cases reported in which concomitant use of amphotericin and hydrocortisone was followed by cardiac enlargement and congestive failure. Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, retention of salt and water, and increased excretion of potassium, but these effects are less likely to occur with synthetic derivatives, except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.
The slower rate of absorption by intramuscular administration should be recognised. In patients on corticosteroid therapy subjected to unusual stress (e.g. intercurrent illness, trauma, or surgical procedures), dosage should be increased before, during and after the stressful situation.
Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimised by gradual dosage reduction, being tapered off over weeks and months depending on the dose and duration of treatment, but may persist for months after discontinuation of therapy. In any stressful situation during that period, therefore, corticosteroid therapy should be reinstated.
If the patient is already receiving corticosteroids, the dosage may have to be increased. Salt and/or a mineralocorticoid should be given concurrently, since mineralocorticoid secretion may be impaired.
Stopping corticosteroids after prolonged therapy may cause withdrawal symptoms including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.
Patients should carry steroid treatment cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.
Because anaphylactoid reactions have occurred, rarely, in patients receiving parenteral corticosteroid therapy, appropriate precautions should be taken prior to administration, especially when the patient has a history of allergy to any drug.
Administration of live virus vaccines is contra-indicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals 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.
Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

The use of DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP 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 antituberculosis regimen. If the corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation may occur. During prolonged corticosteroid therapy, these patients should receive prophylactic chemotherapy.
Corticosteroids 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 infections and their severity. The clinical presentation may often be atypical, and serious infections such as septicaemia and tuberculosis may be masked and reach an advanced stage before being recognised. There may be decreased resistance, and inability to localise infection. A report shows that the use of corticosteroids in cerebral malaria is associated with a prolonged coma and an increased incidence of pneumonia and gastro-intestinal bleeding. Chickenpox is of particular 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 immunisation with varicella/zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.
Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. Exposed patients should be advised to seek medical advice without delay.
Corticosteroids may activate latent amoebiasis or strongyloidasis or exacerbate active disease. Therefore, it is recommended that latent or active amoebiasis and strongyloidiasis be ruled out before initiating corticosteroid therapy in any patient at risk of or with symptoms of either condition. Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses. Corticosteroids may increase or decrease motility and number of spermatozoa.

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 (see "side-effects" section).

Special precautions: Particular care is required when considering use of systemic corticosteroids in patients with the following conditions, and frequent patient monitoring is necessary: renal insufficiency, hypertension, diabetes or in those with a family history of diabetes, congestive heart failure, osteoporosis, previous steroid myopathy, glaucoma (or family history of glaucoma), myasthenia gravis, non-specific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer existing or previous history of severe affective disorders (especially previous steroid psychosis), liver failure, and epilepsy. Signs of peritoneal irritation following gastro-intestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism. There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.
Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.
Local steroid injection should be undertaken in an aseptic environment to reduce the particular risk of

bacterial infection. Injection of a steroid into an infected site should be avoided. Appropriate examination of joint fluid is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Patients should understand the great importance of not over-using joints that are still diseased despite symptomatic improvement. Corticosteroids should not be injected into unstable joints. Frequent intra-articular injections have been reported to cause development of Charcot-like arthropathies.

Visual disturbance : Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Children: Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimise suppression of the hypothalamo-pituitary-adrenal axis and growth retardation, treatment should be limited, where possible, to a single dose on alternate days. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored.

Use in pregnancy and lactation

There is inadequate evidence of safety in human pregnancy and there may be a very small risk of cleft palate and intra-uterine growth retardation in the fetus; there is evidence of harmful effects on pregnancy in animals. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Patients with pre-eclampsia or fluid retention require close monitoring. Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacological doses of corticosteroids should be advised not to breast-feed.

Drug interactions

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia. The renal clearance of salicylates is increased by corticosteroids and therefore salicylate dosage should be reduced along with steroids withdrawal. As phenytoin, barbiturates, ephedrine, rifabutin, carbamazepine, rifampicin, and aminoglutethimide may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and reduced physiological activity, the dosage may have to be adjusted. These interactions may interfere with dexamethasone suppression tests, which should be interpreted with caution during administration of these drugs. False-negative results in the dexamethasone suppression test in patients being treated with indomethacin have been reported. The efficacy of coumarin anticoagulants may be changed by concurrent corticosteroid treatment. The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time, in order to avoid spontaneous bleeding. The desired effects of hypoglycaemic agents (including insulin), are antagonised by corticosteroids. When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalaemia.
Corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false-negative results.

Side-effects

The incidence of predictable undesirable effects, including hypothalamic-pituitary- adrenal suppression, correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see 'Precautions').

Fluid and electrolyte disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalaemic alkalosis, hypertension, increased calcium excretion (see 'Precautions').

Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis (especially in post-menopausal females), vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture, and post- injection flare (following intra-articular use).

Gastro-intestinal: Peptic ulcer with possible perforation and haemorrhage, perforation of the small and large bowel, particularly in patients with inflammatory bowel disease, pancreatitis, abdominal distension, ulcerative oesophagitis, dyspepsia, oesophageal candidiasis.

Dermatological: Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, striae, telangiectasia, acne, increased sweating, possible suppression of skin tests, burning or tingling especially in the perineal area (after intravenous injection), other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic oedema, and hypo- or hyper- pigmentation.

Neurological: Convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment, vertigo, headache, psychic disturbances (e.g. euphoria, psychological dependence, depression, insomnia).

Psychiatric disorders: Depression, irritation, euphoria, thymoleptic and appetizing effect, psychosis, sleep disorders.

Endocrine: Menstrual irregularities, amenorrhoea, development of Cushingoid state, suppression of growth in children and adolescents, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress) as in trauma, surgery or illness, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycaemic agents in diabetes, hirsutism, pheochromocytoma crisis.

Anti-inflammatory and immunosuppressive effects: Increased susceptibility and severity of infections with suppression of clinical symptoms and signs. Opportunistic infections, recurrence of dormant tuberculosis (see 'Precautions').

Ophthalmic: Posterior subcapsular cataracts, increased intra-ocular pressure, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral disease, glaucoma, exophthalmos, rare instances of blindness associated with intra-lesional therapy around the face and head, retinopathy of prematurity, vision blurred.

Metabolic: Negative nitrogen balance due to protein catabolism. Negative calcium balance.

Cardiovascular: Myocardial rupture following recent myocardial infarction (see 'Precautions'). Hypertrophic cardiomyopathy in low birth-weight infants.

Other: Hypersensitivity, including anaphylaxis has been reported, leucocytosis, thrombo- embolism, weight gain, increased appetite, nausea, malaise, hiccups and sterile abscess.

Withdrawal symptoms and signs: Too rapid reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension, and death (see 'Precautions').

In some instances, withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been undergoing treatment.

Overdosage

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. No antidote is available. Treatment is probably not indicated for reactions due to chronic poisoning unless the patient has a condition that would render a patient unusually susceptible to ill effects from corticosteroids. In this case symptomatic treatment should be instituted as necessary. Anaphylactic and hypersensitivity reactions may be treated with adrenaline, positive-pressure artificial respiration and aminophylline. The patient should be kept warm and quiet.

The biological half-life of dexamethasone in plasma is about 190 minutes.

Pharmaceutical precautions

DEXAMETHASONE SODIUM PHOSPHATE INJECTION USP is sensitive to heat and should not be autoclaved to sterilise the outside of the ampoule/vial.

Store below 25 °C, protected from light. Only sodium chloride injection or dextrose injection should be used as diluent. Any infusion mixture must be used within 24 hours.

Packing:

10 ampoules x 1 mL

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Manufactured by:

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GERMANY

PANPHARMA