DEXALONE

Dexamethasone

Dexalone Tablet 0.5
A 6.5 mm diameter, round, flat, scored, white tablet.
Each tablet contains Dexamethasone 0.5 mg

Dexalone Tablet 0.75
An oval shape, scored, white tablet.
Each tablet contains Dexamethasone 0.75 mg

INDICATIONS
Dexamethasone is indicated for treatment of adrenocortical function abnormalities, allergic disorders, collagen disorders, dermatologic disorders, gastrointestinal disorders, haematologic disorders, prophylaxis of cancer chemotherapy-induced nausea and vomiting, hypercalcaemia associated with neoplasms, nonrheumatic inflammation, neoplastic disease, neurologic disease, neurotrauma, ophthalmic disorders, oral disorders, pericarditis, nasal polyps, respiratory disorders, rheumatic disorders, nonsuppurative thyroiditis, organ transplant rejection and trichinosis. Dexamethasone is also indicated in the diagnosis of Cushing's syndrome and to distinguish Cushing's syndrome caused by excessive corticotropin secretion from that due to other causes and diagnosis and evaluation of the efficacy of treatment in endogenous depression.

PHARMACODYNAMICS
Dexamethasone diffuses across cell membranes and complex with specific cytoplasmic receptors which then enter the cell nucleus, bind to DNA, and stimulate transcription of messenger RNA (mRNA) and subsequently protein synthesis of various enzymes thought to be ultimately responsible for glucocorticoid effects of systemic corticosteroids.
Dexamethasone decreases or prevents tissue responses to inflammatory processes, thereby reducing development of symptoms of inflammation without affecting the underlying cause. Dexamethasone inhibits accumulation of inflammatory cells, including macrophages and leukocytes, at sites of inflammation. It also inhibits phagocytosis, lysosomal enzyme release, and synthesis and/or release of several chemical mediators of inflammation. Although the exact mechanisms are not completely understood, actions that contribute significantly to these effects include blockade of the action of macrophage inhibitory factor (MIF), leading to inhibition of macrophage localisation; reduction of dilatation and permeability of inflamed capillaries and reduction of leukocyte adherence to the capillary endothelium, leading to inhibition of both leukocyte migration and edema formation; and increased synthesis of lipomodulin (macrocortin), and inhibitor of phospholipase A2-mediated arachidonic acid release from membrane phospholipids, with subsequent inhibition of the synthesis of arachidonic acid-derived mediators of inflammation (prostaglandins, thromboxanes, and leukotrienes). Immunosuppresant actions may also contribute significantly to the anti-inflammatory effect. Mechanisms of immunosuppresant action are not completely understood but may involve prevention or suppression of cell-mediated (delayed hypersensitivity) immune reactions as well as more specific actions affecting the immune response.Dexamethasone reduces the concentration of thymus-dependent lymphocytes (T -lymphocytes), monocytes, and eosinophils. It also decreases binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T -lymphocyte blastogenesis and reducing expansion of the primary immune response. Dexamethasone may also decrease passage of immune complexes through basement membranes and decreases -concentrations of complement components and immunoglobulins. Dexamethasone also inhibits corticotropin secretion, leading to suppression of adrenal hypersecretion of androgens responsible for the androgenism associated with various enzyme deficiencies; reduces plasma calcium concentration by decreasing gastrointestinal absorption of calcium, probably by interfering with intestinal calcium transport (by decreasing the effect of vitamin D), and increasing calcium excretion; and induces enzymes which accelerate or increase production of lung surfactant by type 2 pneumonocytes. Pharmacologic (supraphysiologic) doses of exogenous dexamethasone produces hypothalamic- pituitary-adrenal (HPA) axis suppression via a negative feedback mechanism, i.e., it inhibits pituitary ACTH secretion, thereby reducing ACTH-mediated production of corticosteroids and androgens in the adrenal cortex. It stimulates protein catabolism and induce enzymes responsible for metabolism of amino acids. It decreases synthesis and increases degradation of protein in lymphoid tissue, connective tissue, muscle and skin. With prolonged use, atrophy of these tissues may occur. Dexamethasone also increases glucose availability by inducing hepatic enzymes involved in gluconeogenesis, stimulating protein catabolism (which increases hepatic concentrations of amino acids required for gluconeogenesis), and decreasing peripheral utilisation of glucose. These actions lead to increased hepatic glycogen storage, increased blood glucose concentrations and insulin resistance. It increases lipolysis and mobilises fatty acids from adipose tissues, leading to increased plasma fatty acid concentrations. With prolonged use, an abnormal redistribution of fat may occur. Dexamethasone decreases bone formation and increases bone resorption. It reduces plasma calcium concentrations, leading to secondary hyperparathyroidism and subsequent stimulation of osteoclasts, and directly inhibit osteoblasts. These actions, together with a decrease in the protein matrix of bone secondary to increased protein catabolism, may lead to inhibition of bone growth in children and adolescents and the development of osteoporosis at any age.

PHARMACOKINETICS
Dexamethasone is rapidly and almost completely absorbed from the gastrointestinal tract. It is rapidly distributed to all body tissues. It crosses the placenta and may be excreted in small amounts in breast milk. Most dexamethasone in the circulation is extensively bound to plasma proteins, mainly to globulin and less so to albumin. Dexamethasone is primarily metabolised in the liver but also in the kidney and tissue; mostly to inactive metabolites, which are then excreted renally. Clearance in premature neonates is reported to be proportional to gestational age with a reduced elimination rate in the most premature. Peak effects occur 1-2 hours following oral administration. It has a plasma half-life of 3-4.5 hours but its duration of action depends upon the biological (tissue) half-life, which ranges from 36-54 hours. Therefore, its effects may last for up to 2.75 days.

DOSAGE

	Dexalone Tablet 0.5	***Dexalone Tablet 0.75***
Adult	0.5-9 mg (1-18 tablets) daily as a single dose or in divided doses.	0.5-9 mg (1-12 tablets) daily as a single dose or in divided doses.
Dexamethasone suppression test *Test for Cushing's syndrome*	1 mg (2 tablets) as a single dose at 11.00 p.m. OR 0.5 mg (1 tablet) every 6 hours for 48 hours.	1 mg as a single dose at 11.00 p.m. OR 0.5 mg every 6 hours for 48 hours.
Test to distinguish Cushing's syndrome due to pituitary ACTH hours excess from Cushing's syndrome due to other causes.	2mg (4 tablets) every 6 hours for 48 hours.	2mg every 6 hours for 48 hours
Depression diagnosis	1 mg (2 tablets) as a single dose at 11.0p.m.	1 mg as a single dose at 11.0p.m.
Cerebral edema associated with recurrent or inoperable brain tumour	2 mg (4 tablets) 2-3 times daily, administered as maintenance therapy after cerebral edema has initially been controlled using parenteral dexamethasone sodium phosphate.	2 mg 2-3 times daily, administered as maintenance therapy after cerebral edema has initially been controlled using parenteral dexamethasone sodium phosphate.
Pediatric *Adrenocortical insufficiency*	0.0233 mg/kg of body weight OR 0.67 mg/square meter of body surface daily in 3 divided doses.	
Other indications	0.0833-0.3333 mg/kg of body weight OR 2.5-10 mg/square meter of body surface daily in 3-4 divided doses.	

ROUTE OF ADMINISTRATION:
Oral

SIDE EFFECTS
Increased appetite, indigestion, nervousness or restlessness and trouble in sleeping occurs frequently. Cataracts, diabetes mellitus, changes in skin colour or hypopigmentation, dizziness or lightheadedness, flushing of face or cheeks and unusual increase in hair growth on body or face have been reported. Generalised allergic reaction, sudden blindness, psychic disturbances such as delirium, disorientation, euphoria, hallucinations, manic-depressive episodes, mental depression, paranoia, and increased coagubility of the blood have occur rarely.

Long-term use
Side effects which occur principally during long-term use include acne or other skin problems, avascular necrosis, Cushing's syndrome, edema, endocrine imbalance, gastrointestinal irritation, hypokalaemic syndrome, osteoporosis or bone fractures including vertebra! compression and long bone pathologic fractures, pancreatitis, peptic ulceration or intestinal perforation, steroid myopathy, striae, unusual bruising and impaired wound healing.

Withdrawal syndrome
The use of pharmacological doses of dexamethasone to treat disease suppresses the endogenous secretion of corticotrophin by the anterior pituitary, with the result that the adrenal cortex becomes atrophied. Sudden withdrawal or reduction in dosage may precipitate acute adrenal insufficiency. Symptoms of adrenal insufficiency include malaise, muscle weakness, muscle or joint pain, abdominal or back pain, dizziness, fainting, low-grade fever, prolonged loss of appetite, nausea, vomiting, shortness of breath, frequent or continuing unexplained headaches, unusual tiredness or weakness, rapid weight loss, hypoglycaemia, hypotension and dehydration. Reappearance of disease may also occur.

CONTRAINDICATIONS
Dexamethasone is contraindicated in the presence of acute infections because of interference with inflammatory and immunological responses.

PRECAUTIONS
Dexamethasone should be used cautiously in patients with acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection due to the possible increased risk of severe uncontrollable infections and/or neoplasms. Caution is also recommended in patients with recent intestinal anastomoses, cardiac disease, congestive heart failure, hypertension or renal function impairment as edema may be hazardous. Patients undergoing dialysis may have increased risk of avascular necrosis with long-term dexamethasone use. Patients with existing or recent exposure to chickenpox or measles may be at risk of developing severe, potentially fatal, generalised disease. Extra care is needed to avoid exposure to these infections while prophylatic therapy with VZIG or IGIV or IGIM may be indicated in exposed patients, therapy with an antiviral agent may be

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indicated if chickenpox develops. Symptoms of progression or reactivation of nonspecific ulcerative colitis, diverticulitis, esophagitis, gastritis or peptic ulcer may be masked by dexamethasone; haemorrhage and/or perforation may occur without warning. Dexamethasone may also exarcebate diabetes mellitus, systemic fungal infections, open-angle glaucoma, systemic or uncontrolled viral or bacterial infections and osteoporosis. Patients with hepatic function impairment, hypoalbuminaemia, hepatic cirrhosis and nephrotic syndrome may be at increased risk of dexamethasone toxicity due to reduced availability of albumin for dexamethasone binding leading to increased serum concentrations of unbound drug.

Dexamethasone should also be used with care in patients with ocular herpes simplex (risk of possible corneal perforation), oral herpetic lesions, hyperlipidaemia, hyper- and hyothyroidism. Muscle weakness in patients with myasthenia gravis may be increased initially, possibly leading to respiratory distress; patient should be hospitalised, and respiratory support should be immediately available when dexamethasone therapy is instituted. Dexamethasone may increase risk of aseptic necrosis in patients with systemic lupus erythematosus and may exarcebate or reactivate active and latent tuberculosis.

Blood or urine glucose concentrations and glucose tolerance test may be required for patients with diabetes mellitus or a predisposition to diabetes mellitus. Growth and development determinations are recommended in children and adolescents receiving prolonged therapy. Ophthalmologic examinations may be required at periodic intervals for adults and children receiving therapy for more than 6 weeks to detect the presence of cataracts, increased intraocular pressure, galucoma or ocular infections. Serum electrolyte determinations and stool tests for occult blood loss may be required during long-term therapy.

False positive results in dexamethasone suppression tests for endogenous depression result from chronic alcohol abuse, glutethimide, meprobamate, methaqualone, methyprylon, ephedrine, high doses of estrogens, hepatic enzyme-inducing agents, adrenal hyperfunction (Cushing's disease), anorexia nervosa or malnutrition leading to extreme weight loss, disseminated carcinoma with concurrent serious infection, cardiac failure, dehydration, unstable diabetes mellitus, fever, hypertension, pregnancy, renal failure and temporal lobe disease. On the other hand, false-negative results are obtained with concurrent high doses of benzodiazepines, cyproheptadine, long-term glucocorticoid therapy, indomethacin, adrenal insufficiency and hypopituitarism. The test may also be affected by psychiatric disorders such as acute psychosis, mania, chronic schizophrenia, and primary degenerative dementia. Ephedrine, high doses of estrogens and hepatic enzyme-inducing agents may also cause false-positive results in tests for Cushing's disease. Uptake of sodium pertechnetate Tc 99m, technetium Tc 99m gluceptate, or technetium Tc 99m pentetate into cerebral tumours in brain imaging may be decreased in patients receiving large doses of dexamethasone because of dexamethasone-induced reduction of peritumour edema. Skeletal imaging using technetium Tc 99m medronate, technetium Tc 99m oxidronate, or technetium Tc 99m pyrophosphate may be affected as long-term use of dexamethasone may induce bone calcium depletion, causing decreased bone uptake of these diagnostic agents. Gonadorelin test for hypothalamic-pituitary-gonadal axis function test result may be altered. False-negative test results may occur with nitroblue-tetrazolium test for bacterial infection. Pharmacologic doses of dexamethasone may reduce the thyroid-stimulating hormone (TSH) response to protirelin. Skin tests reactions, including tuberculin and histoplasmin skin tests and patch test for allergy may be suppressed, especially with daily administration of large doses of dexamethasone. Thyroid 1-123 or 1-131 uptake may be decreased. Adrenal function as assessed by ACTH stimulation or measurement of plasma or urinary free cortisol; basophil, eosinophil, lymphocyte and monocyte counts may be decreased. Serum calcium and potassium concentrations and urinary 17-Hydroxysteroid (17-0HCS) and 17-Ketosteroid (17-KS) may be decreased while serum concentrations of cholesterol, lipid, glucose, sodium and uric acid may be increased. Polymorphonuclear leukocyte count may be increased but platelet count may be increased or decreased.

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.

PREGNANCY AND LACTATION

Fertility

Dexamethasone has been reported to increase or decrease the number or motility of spermatozoa. However, it is not known whether reproductive capacity in humans is adversely affected.

Pregnancy

Dexamethasone crosses the placenta. Although adequate studies have not been done in humans, there is some evidence that pharmacologic doses of dexamethasone may increase the risk of placental insufficiency, decreased birthweight, or stillbirth. However, teratogenic effects in humans have not been confirmed. Infants born to mothers who have received substantial doses of dexamethasone during pregnancy should be carefully observed for signs of hypoadrenalism and replacement therapy administered as required. Prenatal administration of dexamethasone to the mother to prevent respiratory distress syndrome in the premature neonate has not been shown to affect the child's growth or development adversely. Physiologic replacement doses of dexamethasone administered for treatment of maternal adrenal insufficiency are also unlikely to adversely affect the foetus or neonate. Studies in animals have shown that dexamethasone increases the incidence of cleft palate, placental insufficiency, spontaneous abortions, and intrauterine growth retardation.
(FDA Pregnancy Category C)

Breast-feeding

Problems in humans have not been documented. Administration of physiologic doses or low pharmacologic doses is not likely to affect the infant adversely. However, breast-feeding during the use of higher pharmacologic doses is not recommended because dexamethasone is excreted in breast milk and may cause unwanted effects, such as growth suppression and inhibition of endogenous steroid production, in the infant.

DRUG INTERACTIONS

Induction of hepatic enzymes by dexamethasone may increase the formation of a hepatotoxic acetaminophen metabolite, thereby increasing the risk of hepatotoxicity. Estrogens may increase the therapeutic and/or toxic effects of dexamethasone while possibility of cardiac arrhythmias or digitalis toxicity is increased by dexamethasone. Hepatic enzyme inducers such as barbiturates, carbamazepine, phenytoin, primidone and rifampicin may increase metabolism of dexamethasone.

Risk of gastrointestinal ulceration or haemorrhage may be increased when alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants or thrombolytic agents are used concurrently with dexamethasone. However concurrent use of NSAIDs in the treatment of arthritis may provide additive therapeutic benefit and permit dexamethasone dosage reduction while effects of coumarin or indandione derivatives are usually decreased. Concurrent chronic use of antacids with dexamethasone may decrease absorption of dexamethasone. Aminoglutethimide and mitotane suppress adrenal function so that glucocorticoid supplementation may be required. Aminoglutethimide also accelerates the metabolism of dexamethasone to reduce its half-life. Carbonic anhydrase inhibitors increase calcium excretion; risk of hypocalcaemia and osteoporosis is increased. Concurrent use with acetazolamide sodium, sodium-containing medications or foods, anabolic steroids and androgens may increase the risk of edema because dexamethasone causes sodium and fluid retention. These effects may also decrease the natriuretic and diuretic effects of diuretic agents.

Dexamethasone may increase blood glucose concentrations; dosage adjustments of oral hypoglycaemic agents or insulin may need to be adjusted. Changes in thyroid status of the patient that may occur as a result of administration, changes in dosage or discontinuation of thyroid hormones or antithyroid agents may necessitate adjustment of dexamethasone dosage. Due to the effects of dexamethasone on serum potassium concentration, use of dexamethasone concomitantly with parenteral amphotericin B, carbonic anhydrase inhibitors, potassium-depleting diuretics, potassium-sparing diuretics, nondepolarising neuromuscular blocking agents, and potassium supplements is not recommended. Risk of infections and possibility of the development of lymphomas or other lymphoproliferative disorders may be increased with use of immunosuppressant doses of dexamethasone in conjunction with other immunosuppressants. Administration of live virus vaccines to patients receiving immunosuppressant doses of dexamethasone may potentiate replication of the vaccine virus, thereby increasing the risk of the patient's developing the viral disease, and/or decreases the patient's antibody response to the vaccine and is not recommended; immunisation with oral polio virus vaccine should be postponed in persons in close contact with the patient. Other immunisations are not recommended in patients receiving immunosuppressant doses of dexamethasone due to the increased risk of neurological complications and the possibility of decreased or absent antibody response. Inhibition of the growth response to somatrem or somatropin may occur with daily doses (per square meter of body surface) in excess of 375-563 mcg of dexamethasone. Concurrent use of dexamethasone with ephedrine, folic acid, mexiletine, ritodrine, salicylates and streptozocin is also not recommended. Co-treatment with CYP3A4 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.

OVERDOSAGE

The adverse effects of dexamethasone are nearly always due to their use in excess of normal physiological requirements. They should be treated symptomatically, where possible the dosage being reduced or the drug slowly withdrawn. Recommended treatment include administrations of antacids between meals to relieve indigestion or mild gastrointestinal irritation that may occur. However, the efficacy of antacids or other antiulcer medications in preventing severe gastrointestinal problems, such as ulceration, haemorrhage, and/or bowel perforation during corticosteroid therapy has not been established. Dosage of dexamethasone should be reduced or therapy discontinued if mental depression or psychoses occur. A phenothiazine may be administered if necessary; lithium has also been recommended. Some patients require electroconvulsive therapy severe depression persists. Tricyclic antidepressants should not be used since they do not relieve, and may exarcebate, corticosteroid-induced mental disturbances. Prophylactic administration of an antipsychotic agent may be indicated if additional courses of corticosteroid therapy are required by a patient with a history of corticosteroid-induced psychosis. Administration of aspirin or another nonsteroidal anti-inflammatory drug may alleviate some of the symptoms of withdrawal effects due to non-HPA axis suppression.

Up-to-date information on treatment of overdose can be obtained from The National Poison Centre University Sains Malaysia (Tel: 800-8099).

PRESENTATION

Dexalone 0.5: 100 x 10's (Blister)
Dexalone Tablet 0.75mg: 100 x10's, 50 x 10's, 10 x10's (Blister)

STORAGE CONDITIONS AND USER INSTRUCTIONS

Store in a dry place below 30ºC.
Protect from light.
Keep out of reach of children.
Jauhi daripada kanak-kanak.

Shelf life: Please refer to the outer package.
Do not use more medicine than the amount recommended.
Take medicine with meals to lessen gastrointestinal irritation.

Product Registration Holder :
Duopharma Manufacturing (Bangi) Sdn.Bhd.
Lot No. 2, 4, 6, 8 & 10, Jalan P/7, Section 13, Bangi Industrial Estate,
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DUOPHARMA

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