

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone Activase 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg dexamethasone

Excipients with known effect

Each tablet contains 72.5 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, flat bevelled tablets of about 6.0 mm in diameter and 2.5-2.8mm, thickness, debossed 'D' on top and '0.5' underneath on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dexamethasone tablets are used for the treatment of various inflammatory and autoimmune diseases e.g.:

Rheumatism, as pain, stiffness or limitation of motion, especially in the joints and related structures, including muscles, bursae, tendons, fibrous tissue;

Collagen disease, as lupus erythematosus, dermatomyositis, polyarteritis nodosa, thrombotic purpura and rheumatoid arthritis;

Allergies, as status asthmaticus, bronchial asthma, contact dermatitis, inflammatory processes of the eye and its adnexa, severe hypersensitivity reactions to drugs or insect stings, anaphylactic shock, impending allograft rejection;

Primary or secondary adrenocortical insufficiency, and adrenogenital syndromes.

Besides Dexamethasone is used as an adjunct in the control of **cerebral oedema** (not in those cases where the oedema is caused by head injury), for treatment of **lymphocytic leukaemia**, as **anti-emetic** in antineoplastic regimens and for palliative treatment in terminal stages of **neoplastic disease**.

4.2 Posology and method of administration

Method of administration

Glucocorticoids may be administered by a number of routes, depending on the nature of the disease and the condition of the patient. Localised therapy is generally preferred because it minimises adverse effects. When systemic administration is required, the oral route is preferred for ease in regulation of dose and the variety in regimens. Dexamethasone tablets should be taken **orally**, preferably with some fluid.

Posology

The **dosage of Dexamethasone tablets** depends on the severity of the condition and the response of the patient. Undesirable effects, such as suppression of the hypothalamus-pituitary-adrenal (HPA) axis may be minimised by using the lowest effective dose for the minimum period, preferably by taking the tablet(s) in the morning and if disease control will allow alternate day therapy. Systemic dexamethasone administered in the evening is more likely to cause clinically significant HPA suppression. Alternate day dosing is not appropriate for patients with established adrenal insufficiency. Frequent patient review is required to appropriately titrate the dose against disease activity. If no favourable response is noted within a couple of days, continuation of glucocorticoid therapy is undesirable.

Adults

The usual dose in adults is 0.5-10 mg per day. As soon as symptoms diminish, the dose should be reduced under continuous observation of the clinical picture to the lowest possible level, or tapered off completely by following the withdrawal schedule below.

Paediatric population

Dexamethasone should only be administered to children with caution, since glucocorticoids can induce growth retardation. The daily dose should be determined by the physician for each child individually.

Prolonged therapy

During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage.

Withdrawal of prolonged therapy

In patients who have received dexamethasone for more than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out (tapered off over weeks or months) depends largely on whether the disease is likely to relapse as the dose of systemic glucocorticoids is reduced. Clinical assessment of disease activity may therefore be needed during withdrawal. If the disease is unlikely to relapse on withdrawal but there is uncertainty about hypothalamus-pituitary-adrenal (HPA) suppression, the dose of systemic dexamethasone may be reduced rapidly to physiological doses. Once a daily dose of approx. 1 mg dexamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic dexamethasone treatment, which has continued for up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to approx. 6 mg dexamethasone 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 dexamethasone therapy should be considered even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic dexamethasone (or other corticosteroids), particularly if taken for more 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 dexamethasone (or other corticosteroid) therapy.
- Patients receiving doses of systemic dexamethasone higher than approx. 6 mg.
- Patients repeatedly taking doses in the evening.

Patients who, during systemic treatment, encounter stresses such as trauma, surgery or infection and who are at risk of adrenal insufficiency, should receive additional systemic dexamethasone cover during these periods. This includes patients who have finished a course of systemic dexamethasone of less than three weeks duration in the week prior to the stress. Patients on systemic dexamethasone therapy who are at risk of adrenal suppression and are unable to take tablets by mouth should receive parenteral dexamethasone cover during these periods.

Too rapid a reduction of dexamethasone dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. Characteristic symptoms of a "withdrawal syndrome" that may occur are fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- gastric and duodenal ulcer;
- acute infections: viral infections and systemic fungal infections (bacterial infections: see section 4.4);
- parasitic infections;
- vaccination with live vaccines (see section 4.4)

4.4 Special warnings and precautions for use

In post-marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment (see "Withdrawal of prolonged therapy" above). During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Anti-inflammatory/Immunosuppressive effects. Glucocorticoid therapy is non-specific, suppresses the symptoms and signs of disease and decreases the resistance to infections. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised. Strong antimicrobial therapy should accompany glucocorticoid therapy when necessary.

Vaccines should not be given to individuals with glucocorticoid therapy-induced immunosuppression. Vaccination with live vaccines, e.g. Chickenpox is of particular concern. **Chickenpox** is a normally minor illness but 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 immunoglobulin (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 even 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 (IVIG) may be indicated. Exposed patients should be advised to seek medical advice without delay. Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerve and may enhance the establishment of secondary ocular infections due to fungi or viruses.

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.

Pheochromocytoma crisis. 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

Glucocorticoids can cause dose-related growth retardation in infancy, childhood and adolescence, which may be irreversible. Therefore, Dexamethasone should only be used in children with caution.

The common adverse effects of systemic glucocorticoids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin.

Close clinical supervision is required to avoid life-threatening reactions.

Particular care is required when considering the use of systemic glucocorticoids in patients with the following conditions and frequent patient monitoring is necessary:

- Osteoporosis (post-menopausal women are particularly at risk);
- Hypertension or congestive heart failure;
- Diabetes mellitus (or a family history of diabetes);
- History of tuberculosis;
- Glaucoma (or a family history of glaucoma);
- Previous glucocorticoid-induced myopathy;
- Liver failure;
- Renal insufficiency;
- Epilepsy;
- Peptic ulceration.

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 for pharmacokinetic interactions that can increase the risk of side effects), 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.

Patient/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.

Patients/carers should also 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.

Preterm neonates: Available evidence suggests long-term neurodevelopment adverse events after early treatment (< 96 hours) of premature infants with chronic lung disease at starting doses of 0.25mg/kg twice daily.

Dexamethasone Tablets contain lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Rifampin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone and aminoglutethimide enhance the metabolism of glucocorticoids and the therapeutic effects may be reduced.

Dexamethasone is a moderate inducer of CYP 3A4. Co-administration of dexamethasone with other drugs that are metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.

Co-treatment 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.

The desired effects of hypoglycaemic agents (including insulin), antihypertensives and diuretics are antagonised by glucocorticoids.

The effects of anticholinesterases are antagonised by glucocorticoids in myasthenia gravis.

Concurrent use of potassium-depleting diuretics (e.g. acetazolamide, loop diuretics, thiazide diuretics or carbenoxolone) and glucocorticoids may result in severe hypokalaemia.

The efficacy of coumarin anticoagulants may be altered by concurrent glucocorticoid therapy and close monitoring of the International Normalised Ratio or prothrombin time is required.

The renal clearance of salicylates is increased by glucocorticoids and steroid withdrawal may result in salicylate intoxication. Combination of corticosteroids with ulcer-inducing agents (e.g. NSAID's) enhances the risk of peptic ulceration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Dexamethasone readily crosses the placenta.

There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. Studies in pregnant animals administered corticosteroids have shown reproductive toxicity and teratogenicity (see section 5.3).

When administered for prolonged periods or repeatedly during pregnancy, systemic glucocorticoids increase the risk of intra-uterine growth retardation (IUGR). There is no evidence for an increased incidence of IUGR following short-term treatment, such as prophylactic treatment for neonatal respiratory distress syndrome. In this case (to prevent respiratory distress syndrome), glucocorticoids are essential.

Patients with pre-eclampsia or fluid retention require close monitoring. Dexamethasone should, for maternal indications, not be used during pregnancy unless clearly necessary.

Adrenal suppression in the neonate following prenatal glucocorticoid exposure is to be expected.

Breast-feeding

No data are available on the transfer of dexamethasone into breast milk. Because corticosteroids are in general excreted into breast milk, and given the lack of experience, breast feeding is discouraged during Dexamethasone therapy.

As with all medicines, before prescribing systemic glucocorticoids in pregnancy or during lactation, the benefits of treatment should be weighed against the potential risks to both mother and child.

4.7 Effects on ability to drive and use machines

Glucocorticoids may cause mood changes (e.g. euphoria or depression) or visual disturbances. If affected, caution should be exercised in driving and operating machinery.

4.8 Undesirable effects

The incidence of predictable undesirable effects of glucocorticoids correlates with the dosage, timing of administration and duration of treatment. The clinician must balance the therapeutic effects of glucocorticoids with their risk for adverse effects, using the lowest possible effective doses for the shortest possible period of time, preferably by dosing in the morning on an alternate day dosing regimen. Early recognition and appropriate management of adverse effects can minimise the potential severe complications of glucocorticoid therapy.

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%.

System Organ Class	Preferred Term(s) or Lower Level Terms Frequency not known*
Blood and lymphatic system disorders	Leucocytosis
Endocrine disorders	Hypothalamo-pituitary disorder, Adrenal suppression, Cushingoid appearance
Eye disorders	Papilloedema (in children with pseudotumour cerebri, usually after

	withdrawal), Glaucoma, Cataract subcapsular, Corneal thinning, Scleral thinning, Chorioretinopathy, Vision, blurred
Gastrointestinal disorders	Gastric ulcer (haemorrhage), Duodenal ulcer (haemorrhage), dyspepsia, peptic ulcer perforation, Pancreatitis acute
General disorders and administration site conditions	Oedema, Impaired healing
Immune system disorders	Drug hypersensitivity, Anaphylactic reaction, Angioedema
Infections and infestations	Infection (aggravated), opportunistic infection, tuberculosis (reactivated), developing severe Varicella-Zoster Virus Infection, Eye infection viral exacerbated, Eye infection fungal exacerbated, Candidiasis
Injury, poisoning and procedural complications	(Spinal) fracture, Tendon rupture, Contusion
Investigations	Weight increased, Carbohydrate tolerance decreased, Intraocular pressure increased
Metabolism and nutrition disorders	Increased appetite, Diabetes mellitus inadequate control, Lipoprotein deficiency, Calcium deficiency, Sodium retention, Fluid retention, Hypokalaemia, Alkalosis hypokalaemic, in post-marketing experience tumour lysis syndrome (TLS) has been reported very rarely
Musculoskeletal and connective tissue disorders	Growth retardation (infancy, childhood and adolescence), Osteoporosis, Osteonecrosis, proximal Myopathy
Nervous system disorders	Intracranial pressure increased (in children with pseudotumour cerebri, usually after withdrawal), Epilepsy aggravated
Psychiatric disorders	Nervousness, Euphoric mood, Drug dependence, Depression, Insomnia, Schizophrenia aggravated,
Reproductive system and breast disorders	Menstruation irregular, Amenorrhoea
Skin and subcutaneous tissue disorders	Dermatitis allergic, Hirsutism, Skin atrophy, Telangiectasia, Skin striae, Acne
Vascular disorders	Hypertension, Embolism

*The frequency of adverse reactions: not known (cannot be estimated from the available data).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance

Earlsfort Terrace

IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

4.9 Overdose

In animal experiments, the acute toxicity of dexamethasone has been shown to be rather low. Symptoms of acute overdosage that can occur are nausea and vomiting. If vomiting has not yet occurred this can be provoked. For the rest a symptomatic treatment is probably sufficient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, Glucocorticoids, ATC code: H02AB02.

Dexamethasone tablets contains as active ingredient dexamethasone, which is a synthetic glucocorticoid with approximately a 7 times higher anti-inflammatory potency than prednisolone and 30 times that of hydrocortisone.

Glucocorticoids are produced and secreted by the adrenal cortex and are an intrinsic part of the hypothalamus-pituitary-adrenal axis (HPA-axis). In physiological concentrations glucocorticoids, both naturally occurring (hydrocortisone or cortisone) or synthetic (like dexamethasone) exert a broad range of effects on multiple organ systems and tissues; they affect carbohydrate, protein, lipid and calcium metabolism and have effects on fluid and electrolyte balance and are important for support of normal cardiovascular structure and function and the normal function of skeletal muscle.

In target tissues glucocorticoids interact with specific receptor proteins to regulate, via the expression of glucocorticoid-responsive genes, protein synthesis. As a consequence of the time required for changes in gene expression and

protein synthesis, most effects of glucocorticoids are not immediate, but become apparent after several hours. This fact is of clinical significance, because a delay generally is seen before beneficial effects of glucocorticoid therapy are observed. Dexamethasone is therapeutically used mostly because of its anti-inflammatory and immunosuppressive properties. Dexamethasone has virtually no mineralocorticoid activity which makes it suitable for use in patients with cardiac failure or hypertension.

5.2 Pharmacokinetic properties

Absorption

After ingestion, dexamethasone is rapidly and well (around 80%) absorbed. Peak plasma levels are reached between 1 and 2 hours after ingestion.

Distribution

Dexamethasone is bound (up to 77%) by plasma proteins, mainly albumin. There is high uptake of dexamethasone by the liver, kidney and adrenal glands.

Biotransformation and Elimination

Metabolism in the liver is slow and excretion is mainly in the urine, largely as unconjugated steroids. The plasma half-life is 3.0-4.5 hours but, as the effects significantly outlast plasma concentrations of steroids, the plasma half-life is of little relevance and the use of the biological half-life is more applicable. The biological half-life of dexamethasone is 36-54 hours. Therefore, Dexamethasone is especially suitable in conditions where continuous glucocorticoid action is desirable.

5.3 Preclinical safety data

The administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. An increase in pre- and post-implantation loss and a reduction in foetal weight were observed in teratogenicity studies in mice, rats and rabbits receiving dexamethasone by injection. Malformations such as hydrops fetalis, cleft palate, exencephaly and encephalocele were also observed at maternally toxic dose levels. In primates, defects of the central nervous system including a decrease total brain and cerebellar weights were reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container to protect from light and moisture.

6.5 Nature and contents of container

Blister pack: Opaque Poly vinyl coated (PVC) film and Aluminium (Al) foil
Pack sizes:
10, 14, 20, 28, 30, 50, 56, 60, 90 and 100 tablets in blister pack
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited
Boumpoulinas 11
Nicosia
1060
Cyprus

8 MARKETING AUTHORISATION NUMBER

PA1567/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd June 2022

10 DATE OF REVISION OF THE TEXT