PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

DEXAMETHASONE KALCEKS SOLUTION FOR INJECTION/INFUSION 4 MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains dexamethasone sodium phosphate, equivalent to 4 mg dexamethasone phosphate.

Excipient with known effect
Each ml of solution contains about 3 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear, colourless solution free from visible particles.
pH of solution between 7.0 – 8.5

4. CLINICAL PARTICULARS

4.1 Therapeutic 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:

- Acute adrenocortical insufficiency - Addison's disease, bilateral adrenalectomy;
- Relative 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 reinstituted to help cope with stress such as that associated with surgery, trauma, burns, or severe infections where specific antibiotic therapy is available;
- Primary and secondary adrenocortical insufficiency.

Disease therapy
Dexamethasone is indicated for therapy of the following diseases:

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.

Pulmonary disorders: Status asthmaticus, chronic asthma, sarcoidosis, respiratory insufficiency.
Blood disorders: Leukaemia, idiopathic thrombocytopaenic purpura in adults, acquired (autoimmune) haemolytic anaemia.

Rheumatic diseases: Rheumatoid arthritis, osteoarthritis, adjunctive therapy for short-term

administration during an acute episode or exacerbation of rheumatoid arthritis or osteoarthritis.

Skin diseases: Psoriasis, erythema multiforme, pemphigus, neutrophilic dermatitis, localised neurodermatitis, exfoliative dermatitis, sarcoidosis of skin, severe seborrhoeic dermatitis, contact dermatitis.

Gastrointestinal disorders: Ulcerative colitis, regional enteritis.

Oedema: Cerebral oedema associated with primary or metastatic brain tumours, neurosurgery or stroke, oedema associated with acute non-infectious laryngospasm (or laryngitis).

Eye disorders: Allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, chorioretinitis, optic neuritis, anterior ischaemic optic neuropathy.

Neoplastic states: Cerebral neoplasms, hypercalcaemia associated with cancer, leukaemias and lymphomas in adults, acute leukaemia in children.

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. Dexamethasone should not be used as a substitute for normal shock therapy.

4.2 Posology and method of administration

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

Dosage requirements are variable and must be individualised on the basis of the disease being treated and patient response.

Intravenous (IV) and intramuscular administration
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 2 to 6 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 phosphate 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 6 hours until the symptoms of oedema subside (usually after 12 to 24 hours). After 2 to 4 days the dosage should be reduced and gradually stopped over a period of 5 to 7 days. Patients with cerebral malignancy may require maintenance therapy with doses of 2 mg intramuscularly or intravenously 2 to 3 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 7- to 10-day period of intensive therapy, and subsequently reduced to zero over the next 7 to 10 days.

High dose schedule

	Adults	**Children > 35 kg**	**Children < 35 kg**
Initial Dose	50 mg IV	25 mg IV	20 mg IV
1st day	8 mg IV every 2 hours	4 mg IV every 2 hours	4 mg IV every 3 hours
2nd day	8 mg IV every 2 hours	4 mg IV every 2 hours	4 mg IV every 3 hours
3rd day	8 mg IV every 2 hours	4 mg IV every 2 hours	4 mg IV every 3 hours
4th day	4 mg IV every 2 hours	4 mg IV every 4 hours	4 mg IV every 6 hours
5th – 8th day	4 mg IV every 4 hours	4 mg IV every 6 hours	2 mg IV every 6 hours
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 should only be used where acute illness or life-threatening situations exist. Oral therapy should be substituted as soon as possible.

Intra-synovial & 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 3 to 5 days (e.g. for bursae) to once every 2 to 3 weeks (for joints). Frequent intra-articular injection may result in damage to joint tissues.

Site of Injection	Dosage
Large Joints	2 mg to 4 mg
Small Joints	800 micrograms to 1 mg
Bursae	2 mg to 3 mg
Tendon Sheaths	400 micrograms to 1 mg
Soft Tissue Infiltration	2 mg to 6 mg
Ganglia	1 mg to 2 mg

Method of administration
Dexamethasone may be administered intravenously or intramuscularly for systemic effect, or as an intra-synovial or soft tissue injection for local effect.
Contains no antimicrobial agent. For single patient use. Use once only and discard any residue.

4.3 Contraindications

Administration of dexamethasone is contraindicated in the following cases:
- systemic fungal infections, or other systemic infections unless specific anti-infective therapy is

given (see section 4.4);
- hypersensitivity to dexamethasone or other corticosteroids or to any component of the injection;
- administration of live virus vaccines (see section 4.4);
- In patients with myasthenia gravis, peptic ulcer, osteoporosis or psychoses.

4.4 Special warnings and precautions for use

Acute adrenocortical insufficiency
Abrupt discontinuation of treatment lasting for more than 10 days can lead to the onset of acute adrenocortical insufficiency. The dose should therefore be reduced slowly if discontinuation is envisaged. Depending on the dose and duration of therapy, adrenocortical insufficiency caused by glucocorticoid therapy may still persist for several months and, in individual cases, for more than one year after discontinuation of therapy.

If particular physical stress situations (e.g. accident, surgery, childbirth) occur during treatment with dexamethasone phosphate, a temporary dose increase may become necessary. Administration of glucocorticoids may also be required in physical stress situations if adrenocortical insufficiency persists after the end of therapy.

Risk of bacterial, viral, fungal, parasitic and opportunistic infections
Treatment with dexamethasone phosphate can increase the risk of bacterial, viral, fungal, parasitic and opportunistic infections due to the immunosuppressive effect.
Symptoms of a manifest or developing infection can be masked, which may make diagnosis more difficult. Particular caution is required in acute viral infections (hepatitis B, herpes zoster, herpes simplex, varicella, herpetic keratitis). In case of acute and chronic bacterial infections, targeted antibiotic therapy should be used.
Latent infections, such as tuberculosis or hepatitis B, may be reactivated. In patients with a history of tuberculosis, dexamethasone should be used only with tuberculostatic prophylaxis.
In case of systemic mycoses, concomitant antifungal therapy should be used.
In case of certain parasitic diseases (amoebic infection, nematodes), concomitant antiparasitic therapy should be used. In patients with known or suspected threadworm infection, glucocorticoids can lead to activation and proliferation.

Simultaneous use of corticosteroids
Systemic corticosteroids should not be stopped for patients who are already treated with systemic (oral) corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease) but not requiring supplemental oxygen.

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.

Special care is required in the following situations:
- Approximately 8 weeks before and up to 2 weeks after prophylactic vaccinations with live vaccines: The course of viral diseases may be particularly severe in patients treated with dexamethasone. Especially at risk are immunocompromised (immunosuppressed) children, as well as individuals who have not yet had measles or chickenpox. If such individuals come into contact with persons with measles or chickenpox during treatment with dexamethasone, they should consult their physician immediately, who may institute preventive treatment as necessary. See also ‘Vaccinations’ below.
- Osteoporosis: Depending on the dosage and duration of treatment, a negative effect on calcium metabolism must be anticipated; hence, supplementary calcium administration is necessary and vitamin D is recommended. Additional treatment should be considered in patients with pre-existing osteoporosis. In patients with severe osteoporosis, use only in life-threatening situations or over short periods. In elderly patients, a specific benefit/risk analysis should be made and vigilance is required for undesirable effects such as osteoporosis.

- Diabetes mellitus: Clinical surveillance and adjustment of antidiabetic therapy.
- Psychiatric history, including risk of suicide (either past or present): Neurological or psychiatric surveillance is proposed.
- Renal impairment: Concomitant effective therapy of the underlying disease and ongoing monitoring.
- Myasthenia gravis: Initial aggravation of symptoms after corticosteroid administration is possible; hence, careful and cautious selection of the starting dose.

Gastrointestinal disorders
In patients with gastrointestinal ulcers, concomitant treatment with antiulcer agents, as well as careful observation (including X-ray monitoring or gastroscopy) is indicated.

Due to the risk of intestinal perforation, dexamethasone phosphate may be used only when clearly indicated, together with appropriate monitoring, in patients with:
- severe ulcerative colitis with imminent perforation;
- abscess formation or purulent infections;
- diverticulitis;
- intestinal anastomosis (immediately postoperatively).

Signs of peritoneal irritation secondary to gastrointestinal perforation may be absent in patients on high glucocorticoid doses.

Risk of tendon disorders
The risk of tendon disorders, tendinitis and tendon rupture increases with concomitant oral use of fluoroquinolones and corticosteroids.

Vaccinations
Administration of live virus vaccines is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. 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, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy. e.g. for Addison's disease.

Risk of anaphylactic reactions
Severe anaphylactic reactions may occur.

Long-term therapy
In long-term therapy, regular medical check-ups (including ophthalmological check-ups at three-monthly intervals) are indicated; at comparatively high doses, care should be taken to ensure adequate potassium intake and sodium restriction, and serum potassium levels must be monitored.

Pregnancy
Women should notify their physician if they are or become pregnant.

Cardiovascular disorders
Careful surveillance is indicated in patients with severe heart failure.
In case of difficult-to-control hypertension, combined antihypertensive treatment and regular monitoring is required. Bradycardia can occur with high dexamethasone doses.
In patients with heart failure, concomitant effective therapy of the underlying disease and ongoing monitoring is required.

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.

Hypertrophic cardiomyopathy
Hypertrophic cardiomyopathy was reported after systemic administration of corticosteroids including dexamethasone to prematurely born infants. In the majority of cases reported, this was reversible on

withdrawal of treatment. In preterm infants treated with systemic dexamethasone diagnostic evaluation and monitoring of cardiac function and structure should be performed (see section 4.8).

Cerebral oedema or increased intracranial pressure
Corticosteroids should not be used in conjunction with a head injury or stroke since they will probably not be of benefit or may even do harm.

Tumor lysis syndrome (TLS)
In post-marketing experience, tumour lysis syndrome (TLS) has been observed in patients with malignant haematological diseases after the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with a high proliferation rate, high tumour burden and high sensitivity to cytostatics, should be closely monitored and treated with appropriate precautions.

Visual disturbances
Visual disturbances may occur with the systemic and topical use of corticosteroids. If a patient presents with symptoms such as blurred vision or other visual disturbances, consideration should be given to referring the patient to an ophthalmologist for evaluation of possible causes; these may include cataracts, glaucoma or rare diseases, e.g. central serous chorioretinopathy (CSC), which have been reported after the use of systemic or topical corticosteroids.
Special caution should be observed in patients with closed- and open-angle glaucoma. In case of corneal ulceration and injury, close ophthalmological monitoring and therapy is required.

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

Dexamethasone should be used only with extreme caution in patients with infectious diseases, keratitis, epilepsy, abscess or other pyogenic infection).

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

Elderly patients
In elderly patients, a specific benefit/risk analysis should be made and vigilance is required for undesirable effects such as osteoporosis.

Paediatric population
Premature infants: Available data indicate long-term undesirable effects on neuronal development after early treatment (< 96 hours) of premature infants with chronic lung disease at dosages of 0.25 mg/kg twice daily at the start of treatment.
Growing children and adolescents should not be treated unless strictly indicated.

Information related to specific methods of administration
Intramuscular use
DEXAMETHASONE KALCEKS should only be administered intramuscularly in exceptional cases for the following reasons:
– local intolerability and tissue wasting (adipose tissue and muscle atrophy) are possible;
– uncertainty in dosage: initially excessive dose, later insufficient effect.

Intravenous use
With intravenous use, dexamethasone phosphate should be injected slowly (2-3 minutes), as too rapid administration is more likely to result in brief secondary effects in the form of unpleasant tingling or paraesthesia, which are *per se* harmless and last for up to 3 minutes.

Intraarticular administration
Intra-articular injection of corticosteroids may product 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.

Local use
In local use, vigilance is required for possible systemic adverse reactions and interactions.

Excipients
This medicinal product contains about 3 mg sodium per ml of solution, equivalent to 0.15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

As this medicinal product may be diluted with sodium-containing solutions (see section 6.7) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

Digitalis glycosides:	Glycoside effect potentiated due to potassium deficiency
Saluretics:	Additional potassium excretion
Antidiabetics:	Glycaemic reduction decreased
Coumarin derivatives:	Anticoagulant effect attenuated or increased. Dose adjustment is necessary when it is concomitantly administered
Ephedrine:	Corticosteroid effect reduced
Rifampicin, phenytoin, carbamazepine, barbiturates, primidone and other medicinal products that induce CYP3A4:	Corticosteroid effect reduced
Ketoconazole, itraconazole, ritonavir, cobicistat, macrolide antibiotics and other medicinal products that inhibit CYP3A4:	During concomitant treatment with CYP3A inhibitors, including products containing cobicistat, an increased risk of systemic adverse reactions can be anticipated. Such combinations should be avoided, unless the benefit outweighs the increased risk of adverse systemic reactions to corticosteroids; in which case, patients should be monitored for systemic corticosteroid effects
Non-steroidal anti-inflammatory drugs/antirheumatic agents (e.g. salicylates and indometacin):	Increased gastrointestinal ulceration and risk of bleeding
Contraceptives containing oestrogen:	Corticosteroid effect increased
Praziquantel:	Reduction in blood praziquantel concentrations possible
ACE inhibitors:	Increased risk for the onset of blood dyscrasias
Chloroquine, hydroxychloroquine, mefloquine:	Increased risk for the onset of myopathy, cardiomyopathy
Somatropin:	Somatropin effect reduced in long-term administration
Laxatives:	Increased potassium loss
Atropine, other anticholinergics:	Additional increase in intraocular pressure not excluded
Non-depolarising muscle relaxants:	Muscle relaxation may be prolonged
Immunosuppressive agents (ciclosporin):	Increased susceptibility to infections and aggravation or manifestation of latent infections. With ciclosporin, there is an additionally increased risk of cerebral seizures
Bupropion:	Co-administration with systemic glucocorticoids can increase the risk of seizures
Fluoroquinolones:	Risk of tendon disorders, tendonitis and tendon ruptures is increased

Effect on testing methods:
Skin reactions to allergy tests may be suppressed.
Protirelin: The rise in TSH when protirelin is administered may be reduced.

If glucocorticoid treatment is administered 8 weeks before or up to 2 weeks after active immunisation, attenuation or absence of immunisation can be expected.

4.6 Fertility, pregnancy and lactation

Pregnancy
Dexamethasone crosses the placenta. During pregnancy, especially in the first three months, it should only be used after a careful benefit/risk assessment. Dexamethasone should be used during pregnancy only in life-threatening situations. In long-term treatment with glucocorticoids during pregnancy, foetal growth disorders cannot be excluded. Administration of corticosteroids to pregnant animals can cause malformations of foetal development, including cleft palates, intrauterine growth retardation and effects on growth and brain development. There are no indications that corticosteroids lead to an increased incidence of congenital abnormalities such as cleft palate/cleft lip in humans. See also section 5.3. If glucocorticoids are given at the end of pregnancy, there is a foetal risk of adrenocortical atrophy, which may necessitate tapered replacement therapy in the neonate. Studies have shown an increased risk of neonatal hypoglycaemia following antenatal administration of a short course of corticosteroids including dexamethasone to women at risk for late preterm delivery.

Breast-feeding
Glucocorticoids are excreted in human milk. No harm to the infant has been reported to date. Nevertheless, they should be used only when strictly indicated during breast-feeding. If higher doses are required on account of the disease, breast-feeding should be discontinued.

Fertility
No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The risk of undesirable effects is low with short-term dexamethasone therapy. However, vigilance is required for gastrointestinal ulcers (often stress-related) which, as a result of the corticosteroid treatment, may produce few symptoms, as well as for signs of reduced glucose tolerance and resistance to infections.

Especially in long-term treatment (longer than about 2 weeks), adverse reactions to glucocorticoids can occur, which, as an exaggerated hormonal effect, are similar to Cushing's syndrome.

The following adverse reactions may occur, which are highly dependent on the dose and duration of therapy and whose frequency is therefore not known (cannot be estimated from the available data):

Infections and infestations
Masking of infections, manifestation, proliferation or reactivation of infections (bacterial, viral, fungal and parasitic and opportunistic infections), threadworm activation (see section 4.4).

Blood and lymphatic system disorders
Blood dyscrasias (moderate leukocytosis, lymphocytopenia, eosinopenia, polycythaemia).

Immune system disorders
Hypersensitivity reactions (e.g. exanthema), severe anaphylactic reactions such as arrhythmias, bronchospasm, hypo- or hypertension, circulatory collapse, cardiac arrest, weakening of the immune

system.

Endocrine disorders
Cushing's syndrome (e.g. moon face, truncal obesity), adrenocortical inactivation or atrophy.

Metabolism and nutrition disorders
Sodium retention with oedema formation, increased potassium excretion (caution: arrhythmias), weight gain, reduced glucose tolerance, diabetes mellitus, increased appetite, hypercholesterolemia and hypertriglyceridemia.

Psychiatric disorders
Psychosis, depression, irritability, euphoria, sleep disorders, lability, anxiety, mania, hallucinations, suicidal ideation.

Nervous system disorders
Pseudotumor cerebri, manifestation of latent epilepsy and increased seizure susceptibility in cases of manifest epilepsy.

Eye disorders
Increased intraocular pressure (glaucoma), lens opacity (cataract). Aggravation of corneal ulcer symptoms, promotion of viral, fungal and bacterial eye inflammation, aggravation of bacterial inflammation of the cornea, ptosis, mydriasis, chemosis, iatrogenic scleral perforation, chorioretinopathy. In very rare cases, reversible exophthalmos (see also section 4.4).

Cardiac disorders
Hypertrophic cardiomyopathy in prematurely born infants (see section 4.4).

Vascular disorders
Hypertension, increased risk of atherosclerosis and thrombosis, blood vessel inflammation (vasculitis, also as a withdrawal symptom after long-term therapy), capillary fragility.

Gastrointestinal disorders
Stomach upset, activation and development of gastric ulcer or duodenal ulcer, pancreatitis (in predisposed patients, e.g. due to alcoholism), gastrointestinal bleeding, risk of perforation in ulcerative colitis.

Skin and subcutaneous tissue disorders
Stretch marks (striae rubra), skin thinning (atrophy), pinpoint bleeding under the skin (petechiae), bruising (ecchymosis), steroid acne, perioral dermatitis, telangiectasia, hypertrichosis, changes in skin pigmentation.

Musculoskeletal and connective tissue disorders
Muscle weakness, muscle wasting (atrophy), myopathy, tendon disorders, tendinitis, tendon rupture, osteoporosis, aseptic osteonecrosis, growth retardation in children, epidural lipomatosis.

Reproductive system and breast disorders
Disorders of sex hormone secretion (amenorrhoea, hirsutism, impotence).

General disorders and administration site conditions
Delayed wound healing.

Local use: Local irritation and signs of intolerability are possible (sensations of heat, prolonged pain), especially in ocular use. The development of skin atrophy and subcutaneous tissue atrophy at the injection site cannot be excluded if corticosteroids are not injected carefully into the joint cavity.

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 the national reporting system.

4.9 Overdose

There are no known cases of acute intoxication with dexamethasone. In the event of overdose, increased adverse reactions (see section 4.8) can be expected, especially on the endocrine system, metabolism and electrolyte balance. There is no known antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, corticosteroids for systemic use, plain, glucocorticoids, ATC code: H02AB02

Dexamethasone is a monofluorinated glucocorticoid with marked anti-allergic, anti-inflammatory and membrane-stabilising properties, as well as effects on carbohydrate, protein and lipid metabolism.

With a biological half-life of over 36 hours, dexamethasone belongs to the very long-acting glucocorticoids. Due to its long duration of action, dexamethasone can lead to accumulation and overdosing when continuously administered daily.

Dexamethasone possesses a glucocorticoid effect approximately 7.5 times more potent than prednisolone and prednisone; compared with hydrocortisone, it is 30 times more potent; it has no mineralocorticoid effects.

Glucocorticoids such as dexamethasone exert their biological effect by activating the transcription of corticosteroid-sensitive genes. The antiinflammatory, immunosuppressant and antiproliferative effects are induced by factors such as reduced formation, release and activity of inflammatory mediators and by inhibition of specific functions and migration of inflammatory cells. In addition, the effect of sensitised T-lymphocytes and macrophages on target cells by corticosteroids is possibly prevented.

5.2 Pharmacokinetic properties

<u>Distribution</u>
Dexamethasone is dose-dependently bound mainly to plasma albumins. At very high concentrations, the major fraction is available freely in blood, i.e. not bound to proteins. In cases of hypoalbuminemia, the fraction of unbound (active) corticosteroid increases.

Cerebrospinal fluid (CSF) penetrability
In humans, peak dexamethasone CSF levels approximately 1/6 of concomitant plasma concentrations are measured four hours after intravenous administration of radioactively labelled dexamethasone.

Placental transfer
Like all glucocorticoids, dexamethasone can cross the placental barrier but, in contrast to most other corticosteroids, it is not metabolised.

Excretion in human milk
No data are available on dexamethasone. Small amounts of glucocorticoids are excreted in human milk, with infant exposure generally less than 1/100 of the dose systemically available in the breast-feeding mother. Nevertheless, with the use of higher doses or during long-term treatment, breastfeeding should be discontinued.

<u>Biotransformation</u>
Following intravenous injection of dexamethasone phosphate, ester cleavage is very rapid. Peak values

of the free dexamethasone alcohol are measured after 10 minutes.
It is partly metabolised by conjugation with glucuronic or sulphuric acid in the liver with subsequent excretion mainly via the kidneys.

Elimination
The mean serum elimination half-life of dexamethasone in adult humans is 4.1±1.3 hours. Dexamethasone is largely eliminated via the kidneys in the urine as free dexamethasone alcohol. Kidney damage does not significantly affect dexamethasone elimination. In severe hepatic diseases, e.g. hepatitis, cirrhosis of the liver, as well as during pregnancy and oestrogen administration, the elimination half-life of glucocorticoids is prolonged.
In humans, dexamethasone phosphate is mainly excreted as dexamethasone. To a minor extent, the molecules are hydrogenated or hydroxylated, resulting in the main metabolites 6-hydroxydexamethasone and 20-dihydrodexamethasone. In humans, 30-40% of the amount excreted in the urine is bound to glucuronic acid or sulphuric acid.

5.3 Preclinical safety data

Acute toxicity
In mice and rats, the LD_{50} for dexamethasone after a single oral dose is 16 g/kg body weight and over 3 g/kg body weight, respectively, within the first 7 days. Following a single subcutaneous dose, the LD_{50} in mice is more than 700 mg/kg body weight and in rats about 120 mg/kg body weight, within the first 7 days.
Over a period of 21 days, these values become lower, which is interpreted as a consequence of serious infectious diseases caused by the hormone-induced immunosuppression.

Chronic toxicity
There are no data on chronic toxicity in humans and animals. Corticoid-induced intoxications are not known. In longer-term treatment with doses above 1.5 mg/day, pronounced undesirable effects can be expected (see section 4.8).

Mutagenic and carcinogenic potential
The available study findings for glucocorticoids show no evidence of clinically relevant genotoxic properties.

Reproductive toxicity
In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and the heart. In primates, effects in the brain were seen after exposure. Moreover, intra-uterine growth can be delayed. All these effects were seen at high dosages.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Creatinine
Sodium citrate (for pH adjustment)
Disodium edetate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.7.

6.3 Shelf life

2 years

6.4 Shelf life after dilution

Chemical and physical in-use stability has been demonstrated for 48 hours at 25 °C (protected from light) and 2 to 8 °C.
From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Special precautions for storage

Do not store above 25 °C.
Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.4.

6.6 Nature and contents of container

1 ml Type I clear colourless glass ampoules with one point cut.
Ampoules are packed in liners. Liners are packed in outer cartons.

Pack size: 10 ampoules

6.7 Special precautions for disposal and other handling

For single use only.

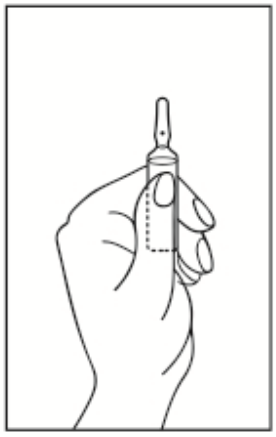
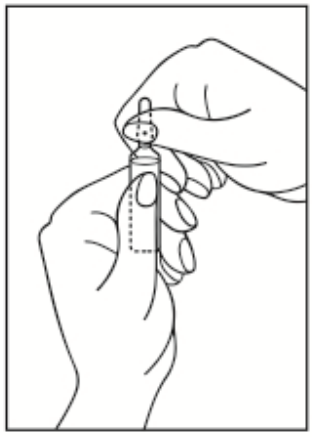
Once opened, the medicinal product should be used immediately. Any remaining contents should be discarded.

The medicinal product should be visually inspected prior to use. Only clear solutions free from particles should be used.

DEXAMETHASONE KALCEKS solution for injection/infusion should preferably be administered by the direct intravenous route or injected into the infusion tube. However, the solutions for injection are compatible with the following solutions for infusion (250 ml and 500 ml):
- 9 mg/ml (0.9%) sodium chloride solution
- 50 mg/ml (5%) glucose solution
- Ringer's solution.

When combining with solutions for infusion, information from the respective manufacturers on their solutions for infusion, including data on compatibility, contraindications, undesirable effects and interaction, must be taken into account.

Instructions for ampoule opening:
1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER AND MANUFACTURER

Product Owner:
AS KALCEKS
Krustpils iela 71E, Rīga, LV-1057, Latvia

Manufacturer:
HBM Pharma s.r.o.
Sklabinska 30, 036 80 Martin, Slovakia

8. MARKETING AUTHORISATION NUMBER(S)

SINXXXXXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

08/2023