1. NAME OF THE MEDICINAL PRODUCT

KRISTEN® 0.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dexamethasone 0.5 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White colour, round, uncoated tablets with cross lines on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, and serum sickness.

Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, and severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; may be used in conjunction with synthetic mineralocorticoid analogs where applicable; in infancy mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, and nonsuppurative thyroiditis.

Gastrointestinal diseases: To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic disorders: Acquired (autoimmune) haemolytic anaemia, congenital (erythroid) hypoplastic anaemia (Diamond-Black fan anaemia), idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, and selected cases of secondary thrombocytopenia.

Miscellaneous: Diagnostic testing of adrenocortical hyperfunction, trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic diseases: For the palliative management of leukaemia and lymphomas.

Nervous system: Acute exacerbations of multiple sclerosis, cerebral oedema associated with primary or metastatic brain tumor, craniotomy, or head injury.

Ophthalmic diseases: Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal diseases: To induce a diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used

concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute rheumatic carditis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

4.2 Posology and method of administration

For oral administration

The initial dosage varies from 0.75 to 9 mg a day depending on the disease being treated.

It Should Be Emphasized That Dosage Requirements Are Variable and Must Be Individualized on The Basis of The Disease Under Treatment and The Response Of The Patient. After a favourable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage that maintains an adequate clinical response is reached.

Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.
In the treatment of acute exacerbations of multiple sclerosis, daily doses of 30 mg ofdexamethasone for a week followed by 4 to 12 mg every other day for one month have been shown to be effective (see PRECAUTIONS, Neuro-psychiatric).

In paediatric patients, the initial dose of dexamethasone may vary depending on the specific disease entity being treated. The range of initial doses is 0.02 to 0.3 mg/kg/day in three or four divided doses (0.6 to 9 mg/m2bsa/day).

For comparison, the following is the equivalent milligram dosage of the various

corticosteroids: Cortisone, 25 Triamcinolone, 4 Hydrocortisone, 20 Paramethasone, 2

Prednisolone, 5 Betamethasone, 0.75 Prednisone, 5 Dexamethasone, 0.75 Methylprednisolone, 4

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active viral disease (especially viral hepatitis, herpes, varicella, shingles). Uncontrolled psychoses.

4.4 Special warnings and precautions for use

Dexamethasone is a glucocorticoid. This should be taken into consideration in the surveillance of the patient. The benefit from dexamethasone treatment should be carefully and continuously weighed against actual and potential risks.

Risk of infection

Treatment with high-dose dexamethasone increases the risk of developing serious infections, due to bacteria, yeasts and/or parasites. Such infections can also be caused by microorganisms that rarely cause disease under normal circumstances (opportunistic infections). Signs of a developing infection may be masked by dexamethasone therapy. Before the start of treatment, any source of infection, especially tuberculosis, should be removed. During treatment, patients should be closely monitored for the appearance of infections. In particular, pneumonia occurs commonly. Patients should be informed of the signs and symptoms of pneumonia and be advised to seek medical attention in case of their appearance. In case of active infectious disease, appropriate anti-infective treatment must be added to the treatment with dexamethasone.

Patients must avoid contact with subjects with chickenpox or measles. Immunocompromised patients who have not previously had chickenpox or measles are particularly at risk. If such patients have been in contact with people with chickenpox or measles, a preventive treatment with intravenous normal immunoglobulin or passive immunisation with varicella zoster immunoglobulin (VZIG) must be started as appropriate. Exposed patients should be advised to seek medical attention without delay.

Vaccinations

Dexamethasone should not be used with live attenuated vaccines (see section 4.5). Vaccinations with inactivated vaccines are usually possible. However, the immune response and hence the effect of the vaccination can be diminished by high glucocorticoid doses.

Interference with laboratory tests

Dexamethasone can suppress skin reaction to allergy testing. It can also affect the nitro blue tetrazolium (NBT) test for bacterial infections and cause false-negative results.

Psychiatric disorders

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 (see also section 4.5 for pharmacokinetic interactions that can increase the risk of adverse reactions), 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. Patients/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 psychoses. Insomnia may be minimised by administering in the morning.

Eye disorders

Systemic treatment with glucocorticoids can induce chorioretinopathy which may result in impaired vision including loss of vision.

Prolonged use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses. Particular care is needed when treating patients with glaucoma (or family history of glaucoma) as well as when treating patients with ocular herpes simplex, because of possible corneal perforation.

Tendonitis

Corticosteroids can favour the development of tendonitis and, in exceptional cases, rupture of the affected tendon. This risk is increased by concomitant use of fluoroquinolones and in patients undergoing dialysis with secondary hyperparathyroidism or after renal transplantation.

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.

Elderly

The common adverse reactions to systemic corticosteroids 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.

Monitoring

Use of corticosteroids requires appropriate monitoring in patients with ulcerative colitis (due to perforation risk), recent intestinal anastomoses, diverticulitis, recent myocardial infarction (risk of left ventricular free wall rupture), diabetes mellitus (or family history), renal insufficiency, hepatic impairment, osteoporosis and myasthenia gravis.

Long-term treatment

During treatment, a diet low in simple sugars and high in protein should be followed due to the hyperglycaemic effect of corticosteroids and their stimulation of protein catabolism with a negative nitrogen balance.

Water and sodium retention is common and can lead to hypertension. Sodium intake should be reduced and blood pressure should be monitored. Particular care is needed when treating patients with renal impairment, hypertension or congestive heart failure. Potassium levels should be monitored during treatment. Potassium supplementation should be given particularly if there is a risk of cardiac arrhythmia or concurrent hypokalaemic medicinal products. Glucocorticoid therapy may reduce the effect of anti-diabetic and antihypertensive treatment. The dose of insulin, oral anti-diabetics and anti-hypertensive medicinal products may have to be increased. Depending on the duration of treatment, calcium metabolism may be impaired. Calcium and vitamin D levels should be monitored. In patients not already prescribed bisphosphonates for multiple myeloma related bone disease, bisphosphonates should be considered, particularly if risk factors for osteoporosis are present.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism.

Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic treatment should be recommended, especially in patients with additional thrombotic risk factors. The decision to take

antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

Pharmacokinetic interactions

Effects of other medicinal products on dexamethasone

Dexamethasone is metabolized via cytochrome P450 3A4 (CYP3A4) and transported by the P-glycoprotein (P-gp, also known as MDR1). Concomitant administration of dexamethasone with inducers or inhibitors of CYP3A4 or P-gp may lead to decreased or increased plasma concentrations of dexamethasone, respectively.

The following combinations require precautions due to changes in dexamethasone pharmacokinetics

− Medicinal products that may reduce dexamethasone plasma concentration:
• Aminogluthetimide, due to a reduction of the efficacy of dexamethasone through an increase of its hepatic metabolism.
• Anticonvulsants that are hepatic enzyme inducers: carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone, due to the reduction of dexamethasone plasma levels and hence its efficacy.
• With rifampicin, due to reduction of dexamethasone plasma concentrations and efficacy by an increase of its hepatic metabolism.
• Topical gastro-intestinal medicinal products, antacids and activated carbon, as well as colestyramine, due to reduction of the intestinal absorption of dexamethasone. The administration of such medicinal products should be separated by at least two hours.
• Ephedrine, due to a reduction in dexamethasone plasma levels by increased metabolic clearance.
− Medicinal products that may increase dexamethasone plasma concentration:
• Aprepitant and fosaprepitant, due to an increase of dexamethasone plasma concentrations by a reduction of its hepatic metabolism.
• Clarithromycin, erythromycin, telithromycin, itraconazole, ketoconazole, posaconazole, voriconazole, nelfinavir, ritonavir: Increased dexamethasone plasma concentration due to reduction of its hepatic metabolism by these enzyme inhibitors.
Pregnancy

Based on human experience, dexamethasone is suggested to cause congenital malformations, particularly intra-uterine growth retardation and rarely neonatal adrenal insufficiency, when administered during pregnancy.

Breast-feeding

Glucocorticoids are excreted in human milk and effects have been shown in breastfed newborns/infants of treated women.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Fertility

Studies in animals have shown reductions in female fertility (see Section 5.3). No data on male fertility are available.

4.7 Effects on ability to drive and use machines

Moderate influence on the ability to drive and use machines.

Dexamethasone may cause confusional state, hallucinations, dizziness, somnolence, fatigue, syncope and blurred vision (see section 4.8). If affected, patients should be instructed not to drive, use machines or perform hazardous tasks while being treated with dexamethasone.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions correspond to the predictable safety profile of glucocorticoids.

Hyperglycaemia, insomnia, muscle pain and weakness, asthenia, fatigue, oedema and weight increase occur very commonly. Less common but serious adverse reactions include: pneumonia and other infections and psychiatric disorders (see section 4.4). In combination with thalidomide or its analogues the most serious adverse reactions were venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism, and myelosuppression, particularly neutropenia and thrombocytopenia (see section 4.4).

The incidence of predictable adverse reactions, including adrenal atrophy, correlates with dose, timing of administration and the duration of treatment (see section 4.4).

System organ class Adverse reactions

Infections and infestations Common: Pneumonia, herpes zoster, upper respiratory tract infection, lower respiratory tract infection, oral candidiasis, oral fungal infection, urinary tract infection, herpes simplex, candida

Elimination

The plasma half-life of dexamethasone is approximately 250 minutes.

5. Preclinical safety data

Glucocorticoids have only weak acute toxicity. No chronic toxicity and carcinogenicity data are available. Genotoxicity findings have been shown to be artefactual. In reproductive toxicity studies in mice, rats, hamsters, rabbits and dogs, dexamethasone has led to embryo-fetal malformations such as increase in cleft palate and skeletal defects; decreases in thymus, spleen and adrenal weight; lung, liver, and kidney abnormalities; and inhibition of growth. Post-natal development assessment of animals treated prenatally presented decreased glucose tolerance and insulin sensitivity, behavioural alterations and decrease in brain and body weight. In males, fertility may be decreased through germ cell apoptosis and spermatogenic defects. Data on female fertility are contradictory.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dicalcium phosphate

Maize Starch

Gelatin

Methyl paraben

Propyl paraben

Sodium Starch Glycolate

Purified Talc

Magnesium stearate

Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Tablets should be kept in the blister package until administration. Individual tablets in intact packaging should be separated from the blister using the perforation, e.g. for use in multi-compartment compliance aids.

6.5 Nature and contents of container

10 x 10 tablets in PVC-Aluminium perforated unit dose blister.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Advise patients to not dispose of unused tablets through household waste or wastewater.

7. MANUFACTURER

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