Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dexliq 4 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 4 mg of dexamethasone (as dexamethasone sodium phosphate).

Excipients with known effect: Each ml of solution also contains 275 mg liquid maltitol (E965), 98 mg sorbitol (E420), 0.2 mg ethanol and 90 mg of propylene glycol (E1520).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution.

A colourless to yellowish solution with a mint odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dexliq is indicated for use in:

Infections and infestations: Tuberculous meningitis, only in conjunction with anti-infective therapy.

Neoplasms benign, malignant and unspecified (including cysts and polyps):

- Palliative treatment of neoplastic diseases.
- Prophylaxis and treatment of emesis induced by cytostatics, emetogenic chemotherapy within antiemetic treatment.
- Treatment of symptomatic multiple myeloma, acute lymphocytic/lymphoblastic leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products.

Blood and lymphatic system disorders: Idiopathic thrombocytopenic purpura in adults.

Immune system disorders: Initial treatment of autoimmune disorders like systemic lupus erythematodes.

Endocrine disorders: diagnostic testing of adrenocortical hyperfunction (dexamethasone suppression test).

Nervous system disorders:
Cerebral oedema (only with symptoms of intracranial pressure evidenced by computerised tomography) caused by a brain tumour, neuro-surgical intervention or cerebral abscess.

Vascular disorders: Active phases of systemic vasculitides like panarteritis nodosa (treatment duration should be limited to two weeks in cases of concomitant positive hepatitis B serology).

Respiratory, thoracic and mediastinal disorders:

- Acute asthma exacerbations when use of an oral corticosteroid is appropriate -Croup.

Skin and subcutaneous tissue disorders: Initial treatment of extensive, severe, acute, skin diseases responding to glucocorticoids, e.g. erythroderma, pemphigus vulgaris.

Musculoskeletal and connective tissue disorders:

- Severe progressive course of active rheumatoid arthritis, e.g. fast proceeding destructive forms and/or extraarticular manifestations.
- Severe systemic course of juvenile idiopathic arthritis (Still's disease). -Myositis

Surgical and medical procedures: Prevention and treatment of postoperative vomiting, within antiemetic treatment.

4.2 Posology and method of administration

Posology
Adults

General considerations:
The dosage should be titrated to the individual response and the nature of the disease. In order to minimise side effects, the lowest effective possible dosage should be used (see section 4.8 'Undesirable Effects').

The initial dosage varies from 0.5 – 9 mg a day depending on the disease being treated. In more severe diseases, doses higher than 9 mg may be required. The initial dosage should be maintained or adjusted until the patient's response is satisfactory. Both the dose in the evening, which is useful in alleviating morning stiffness, and the divided dosage regimen are associated with greater suppression of the hypothalamopituitary-adrenal axis. If satisfactory clinical response does not occur after a reasonable period of time, discontinue treatment with Dexliq and transfer the patient to another therapy.

If the initial response is favourable, the maintenance dosage should be determined by lowering the dose gradually to the lowest dose required to maintain an adequate clinical response. Chronic dosage should preferably not exceed 1.5 mg Dexliq daily.

Patients should be monitored for signs that may require dosage adjustment. These may be changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness and the effect of stress (e.g. surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

If the medicinal product is to be stopped after more than a few days of treatment, it should be withdrawn gradually.

The following equivalents facilitate changing to Dexliq from other glucocorticoids:
Milligram for milligram, dexamethasone is approximately equivalent to betamethasone, 4 to 6 times more potent than methylprednisolone and triamcinolone, 6 to 8 times more potent than prednisone and prednisolone, 25 to 30 times more potent than hydrocortisone, and about 35 times more potent than cortisone.

Long term treatment
For the long-term treatment of several conditions, after initial therapy, glucocorticoid treatment should be switched from dexamethasone to prednisone/prednisolone to reduce suppression on the function of the adrenal cortex.

Acute, self-limiting allergic disorders or acute exacerbations of chronic allergic disorders.
The following dosage schedule combining parenteral and oral therapy is suggested (volumes corresponding to milligrams dexamethasone are indicated on the oral syringe):

First day: Dexamethasone sodium phosphate injection 4 mg or 8 mg intramuscularly.

Second day: 1 mg dexamethasone as Dexliq 4 mg/ml Oral Solution twice a day.

Third day: 1 mg dexamethasone as Dexliq 4 mg/ml Oral Solution twice a day.

Fourth day: 0.5 mg dexamethasone as Dexliq 4 mg/ml Oral Solution twice a day.

Fifth day: 0.5 mg dexamethasone as Dexliq 4 mg/ml Oral Solution twice a day.

Sixth day: 0.5 mg dexamethasone as Dexliq 4 mg/ml Oral Solution.

Seventh day: 0.5 mg dexamethasone as Dexliq 4 mg/ml Oral Solution.

Eighth day: Re-assessment.

This schedule is designed to ensure adequate therapy during acute episodes whilst minimising the risk of overdosage in chronic cases.

Raised intracranial pressure
Initial therapy is usually by injection. When maintenance therapy is required, this should be changed to Dexliq as soon as possible. For the palliative management of patients with recurrent or inoperable brain tumours, maintenance dosage should be calculated individually. A dosage of 2 mg two or three times a day may be effective. The smallest dosage necessary to control symptoms should always be used.

Dexamethasone suppression tests:

1. Tests for Cushing's syndrome:

2 mg dexamethasone as Dexliq 4 mg/ml Oral Solution should be administered at 11 pm. Blood samples are then taken at 8 am the next morning for plasma cortisol determination.

If greater accuracy is required, 0.5 mg dexamethasone as Dexliq 4 mg/ml Oral Solution should be administered every 6 hours for 48 hours. Blood should be drawn at 8 am for plasma cortisol determination on the third morning.

Twenty four hour urine collection should be employed for 17-hydroxycorticosteroid excretion determination.

2. Test to distinguish Cushing's syndrome caused by pituitary ACTH excess from the syndrome induced by other causes:

2 mg dexamethasone as Dexliq 4 mg/ml Oral Solution should be administered every 6 hours for 48 hours. Blood should be drawn at 8 am for plasma cortisol determination on the third morning.

Twenty four hour urine collection should be employed for 17-hydroxycorticosteroid excretion determination.

Paediatric population
Dosage should be limited to a single dose on alternate days to lessen retardation of growth and minimize suppression of hypothalamo-pituitary-adrenal axis.

Elderly
Treatment of elderly patients, particularly if long term, should be planned bearing in mind the more serious consequences of the common side effects of corticosteroids in old age.

Renal and liver impairment
The dose of dexamethasone must be adjusted in patients with kidney or liver insufficiency.

Method of administration (Dexliq)
Oral use.

The medicinal product is supplied with a 3 ml graduated dosing syringe and a "press-in" syringe/bottle adaptor. Each individual graduation is equivalent to 0.5 mg dexamethasone.

4.3 Contraindications

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

Systemic infection unless specific anti-infective therapy is employed.

Systemic fungal infections.

Stomach ulcer or duodenal ulcer.

Infection with tropical worms.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternative days. Frequent patient review is required to appropriately titrate the dose against disease activity. When reduction in dosage is possible, the reduction should be gradual (refer to section 4.2 'Posology and Administration').

Adrenal Suppression
An adrenocortical insufficiency, which is caused by glucocortocoid treatment, can, depending on the dose and length of treatment, remain for many months, and in some cases more than a year, after discontinuation of 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. In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg dexamethasone) for greater than 3 weeks, withdrawal should not be abrupt.

How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal.

If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about hypothalamic-pituitary-adrenal (HPA) suppression, the dose of systemic corticosteroids may be reduced rapidly to physiological doses. Once a daily dose of 1 mg dexamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse.

Abrupt withdrawal of doses of up to 6 mg daily of 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 corticosteroid therapy should be considered even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater 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 corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 6 mg daily of dexamethasone.
- Patients repeatedly taking doses in the evening.

Conditions requiring particular attention

Treatment with Dexliq should only be implemented in the event of the strongest indications and, if necessary, additional targeted anti-infective treatment administered for the following illnesses:

- Acute viral infections (Herpes zoster, Herpes simplex, Varicella, herpetic keratitis)
- HBsAG-positive chronic active Hepatitis
- Approximately 8 weeks prior through 2 weeks after vaccinations with live vaccines
- Systemic mycoses and parisitosis (e.g. nematodes)
- Poliomyelitis

- Lymphadenitis after BCG vaccination
- Acute and chronic bacterial infections
- With a history of tuberculosis (reactivation risk). Use only under tuberculostatic protection

In addition, treatment with Dexliq should only be implemented under strong indications and, if necessary, additional specific treatment must be implemented for:

- Gastrointestinal ulcers
- Severe osteoporosis
- Difficult to regulate high blood pressure
- Difficult to regulate Diabetes mellitus
- Psychiatric disorders (including history)
- Angle closure glaucoma and wide-angle glaucoma
- Corneal ulcerations and corneal injuries
- Severe heart failure

Anaphylactic reaction

Serious anaphylactic reactions may occur.

Tendinitis

The risk of tendinitis and tendon rupture is increased in patients treated concomitantly with glucocorticoids and fluoroquinolones.

Myasthenia gravis

Pre-existing myasthenia gravis may initially deteriorate in the beginning of dexamethasone treatment.

Cerebral oedema or increased intracranial pressure

Corticosteroids should not be used in conjunction with a head injury since they will probably not be of benefit or may even do harm.

Intestinal perforation

Because of the risk of an intestinal perforation, Dexliq must only be used under urgent indication and under appropriate monitoring for:

- Severe ulcerative colitis with threatened perforation
- Diverticulitis
- Entero-anastomosis (immediately postoperative)

Signs of peritoneal irritation after gastrointestinal perforation may be absent in patients receiving high doses of glucocorticoids.

Intercurrent illness and stress

During prolonged therapy, any intercurrent illness, trauma, stress 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.

Patients under stress may require increased doses of corticosteroids prior, during and after the period of stressful situation.

During treatment with Dexliq for specific physical stress conditions (trauma, surgery, childbirth, etc.), a temporary increase in dose may be required. Even in cases of prolonged adrenocortical insufficiency after discontinuation of treatment, the administration of glucocorticoids can be necessary in physically stressful situations. An acute therapy-induced adrenocortial insufficiency can be minimized by slow dose reduction until a planned discontinuation time.

Anti-inflammatory/Immunosuppressive effects/Infection

Corticosteroids may exacerbate systemic fungal infections and should not be used unless they are needed to control drug reactions due to amphotericin. There have also been reports in which concomitant use of amphotericin and hydrocortisone was followed by cardiac enlargement and heart failure.

Administration of live virus vaccines is contra-indicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained.

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may be atypical, and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

Appropriate anti-microbial therapy should accompany glucocorticoid therapy when necessary e.g. in tuberculosis and viral and fungal infections of the eye.

Treatment with Dexliq can conceal the symptoms of an existing or developing infection thereby making a diagnosis more difficult. There may be decreased resistance and inability to localise infection in patients on corticosteroids.

Chickenpox is of particular concern, since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster, and if exposed they should seek urgent medical attention. Passive immunisation with varicella/zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous three months; this should be given within ten days of exposure to chickenpox. *If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.*

Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. Exposed patients should be advised to seek medical advice without delay.

Corticosteroids may activate latent amoebiasis or strongyloidiasis or exacerbate active disease. Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis* or *Toxoplasma*. It is recommended that these are ruled out before initiating corticosteroid therapy particularly in those patients who have spent time in the tropics or those with unexplained diarrhoea.

A report shows that the use of corticosteroids in cerebral malaria is associated with a prolonged coma and an increased incidence of pneumonia and gastro-intestinal bleeding and therefore corticosteroids should not be used in cerebral malaria.

Psychiatric reactions

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 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.

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 psychosis.

Eye disorders

Prolonged use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the optic nerves, chorioretinopathy which may result in impaired vision including loss of vision, 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.

Electrolyte disturbances

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, retention of salt and water, and increased excretion of potassium, but these effects are less likely to occur with synthetic derivatives, except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary with corticosteroid therapy. All corticosteroids increase calcium excretion.

Particular care is needed when treating patients with renal impairment, hypertension and congestive heart failure.

Other precautions

A higher need for insulin, or oral antidiabetics, must be taken into consideration when administering Dexliq to diabetics.

Regular blood pressure monitoring is necessary during treatment with Dexliq, particularly during administration of higher doses and with patients with difficult to regulate high blood pressure.

Because of the risk of deterioration, patients with severe cardiac insufficiency should be carefully monitored.

Bradycardia may occur in patients treated with high doses of dexamethasone.

Caution should be exercised when using corticosteroids in patients who have recently suffered myocardial infarction as myocardial rupture has been reported.

Corticosteroids should be used cautiously in patients with migraine, as corticosteroids may cause fluid retention.

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.

Regular checkups with doctors (including vision checkups in three-month intervals) are advised during long-term treatment with Dexliq.

At high doses, sufficient calcium intake and sodium restriction, as well as serum potassium levels should be monitored. Depending on the length and dosage of the treatment, a negative influence on calcium metabolism can be expected, so that an osteoporosis prophylaxis is recommended. This applies, above all, to co-existing risk factors like familial disposition, increased age, after menopause, insufficient protein and calcium intake, heavy smoking, excessive alcohol intake, as well as insufficient exercise. Prevention consists of sufficient calcium and vitamin D intake and physical activity. Additional medical treatment should be considered in the event of preexisting osteoporosis.

The following risks should be considered upon interruption or discontinuation of long-term glucocorticoid administration:

- Exacerbation or recurrence of the underlying disease, acute adrenal insufficiency, corticosteroid withdrawal syndrome.
- Certain viral diseases (chickenpox, measles) in patients treated with glucocorticoids, may be very severe.
- Children and immunocompromised persons without previous chickenpox or measles infection are particularly at risk. If these people have contact with people infected with measles or chickenpox while undergoing treatment with Dexliq, a preventative treatment should be introduced if necessary.

Withdrawal symptoms

Stopping corticosteroids after prolonged therapy may cause withdrawal symptoms including fever, myalgia, arthralgia and malaise. This may occur in patients even without evidence of adrenal insufficiency.

Preterm neonates

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

Paediatric population

Corticosteroids cause a dose-dependent inhibition of growth in infancy, childhood, and adolescence, which may be irreversible. Therefore, during long-term treatment with Dexliq, the indication should be very strongly presented in children and their growth rate should be checked regularly.

Use in the elderly

The adverse effects of systemic corticosteroids can have serious consequences especially in old age, mainly osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and skin atrophy. Close clinical monitoring is required to prevent life-threatening reactions.

Influence of diagnostic tests

Glucocorticoids can suppress skin reaction to allergy testing. They can also affect the nitroblue tetrazolium test for bacterial infections and cause false-negative results.

Note on doping

The use of doping tests when taking Dexliq can lead to positive results.

Steroid treatment cards

Patients should carry 'steroid treatment' cards, which give clear guidance on the precautions to be taken to minimise risk, and which provides details of prescriber, drug, dosage and the duration of treatment.

Excipient Warnings

This medicinal product contains liquid maltitol and sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
This medicinal product contains small amounts of ethanol, less than 100 mg per 10 mg dexamethasone.
This medicinal product contains propylene glycol. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on dexamethasone

Dexamethasone is metabolised via cytochrome P450 3A4 (CYP3A4). Concomitant administration of dexamethasone with inducers of CYP3A4, such as phenytoin, barbiturates, ephedrine, rifabutin, carbamazepine and rifampicin may lead to decreased plasma concentrations of dexamethasone and the dose may need to be increased. Concomitant administration of inhibitors of CYP3A4 such as ketoconazole, ritonavir and erythromycin may lead to increased plasma concentrations of dexamethasone.

These interactions may also interfere with dexamethasone suppression tests, which therefore should be interpreted with caution during administration of substances that affect the metabolism of dexamethasone.

Ketoconazole may increase plasma concentrations of dexamethasone by inhibition of CYP3A4, but may also suppress corticosteroid synthesis in the adrenal and thereby cause adrenal insufficiency at withdrawal of corticosteroid treatment.

Ephedrine may increase the metabolic clearance of corticosteroids, resulting in decreased plasma levels. An increase of the corticosteroid dose might be necessary.

False-negative results in the dexamethasone suppression test in patients being treated with indometacin have been reported.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Colestyramine: Colestyramine may decrease the absorption of dexamethasone.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Aminoglutethimide: Decrease of dexamethasone efficacy, due to its metabolism increase. An adjustment of dexamethasone dosage may be required.

Gastrointestinal topicals, antacids, charcoal: A decrease in digestive absorption of glucocorticoids has been reported with prednisolone and dexamethasone. Therefore, glucocorticoids should be taken separately from gastrointestinal topicals, antacids or charcoal, with an interval between treatments of at least two hours.

Effects of dexamethasone on other medicinal products

Dexamethasone is a moderate inducer of CYP3A4. Concomitant administration of dexamethasone with substances that are metabolised via CYP3A4 could lead to increased clearance and decreased plasma concentrations of these substances.

The renal clearance of salicylates is increased by corticosteroids and therefore, salicylate dosage should be reduced along with steroidal withdrawal.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids.

The hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics, amphotericin B injection, potassium depleting agents, corticosteroids (glucomineralo), tetracosactide and carbenoxolone are enhanced. Hypokalaemia predisposes to cardiac arrhythmia especially “torsade de pointes” and increases the toxicity of cardiac glycosides. Hypokalemia should be corrected before corticosteroid treatment initiation. In addition, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antiulcer drugs: Carbenoxolone increases the risk of hypokalemia.

Chloroquine, hydroxychloroquine and mefloquine: Increased risk of myopathies and cardiomyopathies.

Concomitant administration of ACE inhibitors creates an increased risk of blood disorders.

The blood pressure-lowering effects of antihypertensive drugs may be affected by corticosteroids. The dose of the anti-hypertensive treatment may have to be adjusted during the treatment with dexamethasone.

The risk of tendinitis and tendon rupture is increased in patients treated concomitantly with glucocorticoids and fluoroquinolones.

Atropine and other anticholinergics: Intraocular pressure increases may be noted during coadministration with dexamethasone.

Non-depolarizing muscle relaxants: the muscle relaxing effect may last longer.

Somatotropin: the effect of the growth hormone can be reduced.

Protirelin: Reduced increase in TSH may be noted during administration of protirelin.

Sultopride has been linked to ventricular arrhythmias, especially torsade de pointes. This combination is not recommended.

Patients taking NSAIDs should be monitored since the incidence and/or severity of gastro-ulceration may increase. Aspirin should also be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia.

Ciclosporin: Increased activity of both ciclosporin and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Thalidomide: Co-administration with thalidomide should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use.

Corticosteroids may affect the nitroblue tetrazolium test for bacterial infection and produce falsenegative results.

Vaccines attenuated live: Risk of fatal systemic disease

Praziquantel: Decrease in praziquantel plasma concentrations, with a risk of treatment failure, due to its hepatic metabolism increased by dexamethasone.

Oral anticoagulants: Possible impact of corticosteroid therapy on the metabolism of oral anticoagulants and on clotting factors. At high doses or with treatment for more than 10 days, there is a risk of bleeding specific to corticosteroid therapy (gastrointestinal mucosa, vascular fragility). Patients taking corticosteroids associated with oral anticoagulants should be closely monitored (biological investigations on 8th day, then every 2 weeks during treatment and after treatment discontinuation).

Insulin, sulfonylureas, metformin: Increase in blood glucose, with sometimes diabetic ketosis, since corticosteroids impair carbohydrate tolerance. Therefore, blood and urine self-monitoring should be reinforced by the patient, in particular at the start of treatment.

Isoniazid: A decrease in plasma isoniazid levels have been reported with prednisolone. The suggested mechanism is an increase in hepatic metabolism of isoniazid and a decrease in the hepatic metabolism of glucocorticoids. Patients taking isoniazid should be closely monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy
Dexamethasone crosses the placenta. Administration of corticosteroids to pregnant animals can cause abnormalities in foetal development, including cleft palate, intrauterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man (see Section 5.3). Long-term or repeated corticosteroid therapy in pregnancy increases the risk of intrauterine growth retardation. In newborns exposed to corticosteroids in the prenatal period, there is an increased risk of adrenal insufficiency, which under normal circumstances undergoes spontaneous postnatal regression, and is rarely of clinical significance. Dexamethasone should be prescribed during pregnancy and particularly in the first trimester only if the benefit outweighs the risks for the mother and child.

Breastfeeding
Glucocorticoids are excreted in breast milk. There is insufficient information on the excretion of dexamethasone in human milk. A risk to the newborns/infants cannot be excluded. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.
A decision on whether to continue/discontinue breast feeding or to continue/discontinue therapy with dexamethasone should be made taking into account the benefit of breast feeding to the child and the benefit of dexamethasone therapy to the woman.

Fertility
No data on the influence of dexamethasone on animal or human fertility are available.

4.7 Effects on ability to drive and use machines

Dexliq has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The incidence of anticipated adverse effects, such as the suppression of the hypothalamic-pituitaryadrenal axis correlates with the relative potency of the substance, dose, time of day of administration and duration of treatment. During a short-term therapy, in compliance with the dosage recommendations and close monitoring of patients, the risk of side effects is low.

The usual side effects of short-term dexamethasone treatment (days/weeks) include weight gain, psychological disorders, glucose intolerance and transitory adrenocortical insufficiency. Long-term dexamethasone treatment (months/years) usually causes central obesity, skin fragility, muscle atrophy, osteoporosis, growth retardation and long-term suprarenal insufficiency (see also section 4.4 Special warnings and precautions for use).

Infections and infestations	Increased susceptibility to, or exacerbation of, (latent) infections with masking of clinical symptoms, opportunistic infections, reactivation of latent tuberculosis, exacerbation of eye infections, candidiasis
Blood and lymphatic system disorders	Leukocytosis, lymphopenia, eosinopenia, polycythemia, abnormal coagulation
Immune system disorders	Hypersensitivity reactions including anaphylaxis, immunosuppression (see also under "Infections and parasitic diseases")
Endocrine disorders	Suppression of the hypothalamic-pituitary-adrenal axis and induction of Cushing's syndrome (typical symptoms: full-moon face, plethora, truncal obesity), secondary adrenal and pituitary insufficiency (especially in stress such as trauma or surgery)
Metabolism and nutrition disorders	Weight gain, negative protein and calcium balance, increased appetite, sodium and water retention, potassium loss (caution: rhythm disorders), hypokalemic alkalosis, manifestation of latent diabetes mellitus, impaired carbohydrate tolerance with increased dose requirements of antidiabetic therapy, hypercholesterolemia, hypertriglyceridaemia
Psychiatric disorders	Psychological dependence, depression, insomnia, aggravated schizophrenia, mental illness, from euphoria to manifest psychosis
Nervous system disorders	Increased intracranial pressure with papilloedema in children (pseudotumor cerebri) usually following discontinuation of treatment; manifestation of latent epilepsy, increased seizures in overt epilepsy, vertigo, headache
Eye disorders	Elevated intraocular pressure, glaucoma, papilloedema, cataract, mainly with posterior subcapsular opacity, corneal and scleral atrophy, increased ophthalmic viral, fungal and bacterial infections, worsening of symptoms associated with corneal ulcers
Cardiac disorders	Cardiac muscle rupture after recent history of myocardial infarction, congestive heart failure in predisposed patients, cardiac decompensation*
Vascular disorders	Hypertension, vasculitis, increased atherosclerosis and risk of thrombosis/thromboembolism (increase in coagulability of blood may lead to thromboembolic complications)
Respiratory, thoracic and mediastinal disorders	Hiccough
Gastrointestinal disorders	Dyspepsia, abdominal distension* , gastric ulcers with perforation and bleeding, acute pancreatitis, ulcerative esophagitis, flatulence, nausea, vomiting
Skin and subcutaneous disorders	Hirsutism, hypertrichosis, skin atrophy, telangiectasia, striae, erythema, steroid acne, petechiae, ecchymosis, allergic dermatitis, urticaria, angioneurotic oedema, thinning hair, pigment disorders, increased capillary fragility, perioral dermatitis, hyperhidrosis
Musculoskeletal and connective tissue disorders	Growth inhibition in infants, children and adolescents, premature epiphyseal closure, osteoporosis, fractures of the spine and long bones, aseptic necrosis of the femoral and the humeral bones, tendon tears, proximal myopathy, muscle weakness, loss of muscle mass
Reproductive system and breast disorders	Irregular menses, amenorrhea, impotence
General disorders and administration site conditions	Delayed wound healing, discomfort, steroid withdrawal syndrome: a too rapid reduction in corticosteroid dose after prolonged treatment can lead to acute adrenal insufficiency, hypotension, and death. A withdrawal syndrome may present with fever, myalgia, arthralgia, rhinitis, conjunctivitis, pain, itchy skin nodules and weight loss.
Injury, poisoning and procedural complications	Reduced response to vaccination and skin tests, tendency to bruise

*see also section 4.4 Special warnings and precautions for use

Description of selected adverse reactions

Adrenocortical insufficiency
An adrenocortical insufficiency, which is caused by glucocorticoid treatment, can, depending on the dose and length of treatment, remain for many months and in some cases more than a year, after discontinuation of treatment (see section 4.4 Special warnings and precautions for use).

Psychological changes
Psychological changes are manifested in various forms, the most common being euphoria. Depression, psychotic reactions and suicidal tendencies may also appear. These illnesses can be serious. Usually they start within a few days or weeks of starting the medicine. They are more likely to happen at high doses. Most of these problems go away if the dose is lowered or the medicine is stopped (see section 4.4 Special warnings and precautions for use).

Infections
Treatment with dexamethasone can conceal the symptoms of an existing, or developing infection thereby making a diagnosis more difficult and can lead to an increased risk of infection (see section 4.4 Special warnings and precautions for use).

Intestinal perforation
Corticosteroids can be associated with an increased risk of colonic perforation in severe ulcerative colitis with threatened perforation, diverticulitis and entero-anastomosis (immediately postoperative).

Signs of peritoneal irritation after gastrointestinal perforation may be absent in patients receiving high doses of glucocorticoids (see section 4.4 Special warnings and precautions for use).

Cardiovascular disorders
Bradycardia, deterioration of severe cardiac insufficiency and difficult to regulate high blood pressure may occur. Caution should be exercised when using corticosteroids in patients who have recently suffered myocardial infarction as myocardial rupture has been reported (see section 4.4 Special warnings and precautions for use).

Paediatric population
Corticosteroids cause a dose-dependent inhibition of growth in infancy, childhood, and adolescence since corticosteroids may give rise to early closing of the epiphyses, which may be irreversible (see section 4.4 Special warnings and precautions for use).

Elderly
The adverse effects of systemic corticosteroids can have serious consequences especially in old age, mainly osteoporosis, hypertension, hypokalemia, diabetes, susceptibility to infection and skin atrophy (see section 4.4 Special warnings and precautions for use).

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

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. No antidote is available. Treatment is probably not indicated for reactions due to chronic poisoning unless the patient has a condition that would render him unusually susceptible to ill effects from corticosteroids. In this case, the stomach should be emptied and symptomatic treatment should be instituted as necessary. Anaphylactic and hypersensitivity reactions may be treated with epinephrine (adrenaline), positive-pressure artificial respiration and aminophylline. The patient should be kept warm and quiet. The biological half life of dexamethasone in plasma is about 190 minutes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02A B02

Dexamethasone is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties and is therefore, particularly suitable for the use in patients with cardiac failure and hypertension. Its anti-inflammatory potency is 7 times greater than prednisolone and, like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.

5.2 Pharmacokinetic properties

Dexamethasone is well absorbed when given by mouth; peak plasma levels are reached between 1 and 2 hours after ingestion and show wide interindividual variations. In healthy subjects a plasma half life of 3-6 hours has been observed, however in studies of patients this can be reduced to under 2 hours. Dexamethasone is bound (to about 77%) to plasma proteins, mainly albumins. Percentage protein binding of dexamethasone, unlike that of cortisol, remains practically unchanged with increasing steroid concentrations. Corticosteroids are rapidly distributed to all body tissues. Dexamethasone is metabolised mainly in the liver but also in the kidney. Dexamethasone and its metabolites are excreted in the urine.

5.3 Preclinical safety data

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 of the heart. In primates, effects in the brain were seen after exposure. Moreover, intrauterine growth can be delayed. All these effects were seen at high dosages.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E1520)
Liquid maltitol (E965)
Mint flavour (peppermint, spearmint, menthol, and ethanol)
Liquid sorbitol (non-crystallising) (E420)
Sodium citrate (E331)
Disodium edetate
Sucralose
Sodium hydroxide (as pH adjuster)
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months

After first opening: 3 months

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from light.

Do not refrigerate.

6.5 Nature and contents of container

Amber (Type III) glass bottle containing 30 ml or 50 ml of oral solution, closed with child-resistant, tamper-evident screw cap with an LDPE liner (seal) and a LDPE adaptor.

Each bottle is delivered with a 3 ml graduated oral dosing syringe. The syringe body and piston are made of LDPE. The syringe is graduated in intervals of 0.5 mg and up to 10 mg.

Pack size: 30 ml or 50 ml. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Laboratoires CTRS
16 Rue Montrosier
92200 Neuilly-sur-Seine
France

8 MARKETING AUTHORISATION NUMBER

PA2137/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th June 2017
Date of last renewal: 24th May 2022

10 DATE OF REVISION OF THE TEXT

November 2023