1 NAME OF THE MEDICINAL PRODUCT

Glensoludex 2 mg soluble tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg dexamethasone as dexamethasone sodium phosphate.

The sodium content of Glensoludex 2 mg soluble tablets is 14.96 mg per tablet.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Soluble tablet

Glensoludex Soluble tablets 2 mg are salmon, oblong tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glensoludex is indicated for use in certain endocrine and non-endocrine disorders, in certain cases of cerebral oedema and for diagnostic testing of adrenocortical hyperfunction.

Endocrine disorders:
Endocrine exophthalmos.

Non-endocrine disorders:
Glensoludex may be used in the treatment of non-endocrine corticosteroid responsive conditions including:

Allergy and anaphylaxis: Anaphylaxis.

Arteritis collagenosis: Polymyalgia rheumatica, polyarteritis nodosa.

Haematological disorders: Haemolytic anaemia (also auto immune), leukaemia, myeloma, idiopathic thrombocytopenic purpura in adults, reticulolymphoproliferative disorders (see also under oncological disorders).

Gastroenterological disorders: For treatment during the critical stage in: ulcerative colitis (rectal only); regional enteritis (Crohn’s disease), certain forms of hepatitis.

Muscular disorders: Polymyositis.

Neurological disorders: Raised intra-cranial pressure secondary to cerebral tumours, acute exacerbations of multiple sclerosis.

Ocular disorders: Anterior and posterior uveitis, optic neuritis, chorioretinitis, iridocyclitis, temporal arteritis, orbital pseudotumour.

Renal disorders: Nephrotic syndrome.
Pulmonary disorders: Chronic bronchial asthma, aspiration pneumonitis, chronic obstructive pulmonary disease (COPD), sarcoidosis, allergic pulmonary disease such as farmer’s and pigeon breeder’s lung, Löffler’s syndrome, cryptogenic fibrosing alveolitis.

Rheumatic disorders: Some cases or specific forms (Felty’s syndrome, Sjögren’s syndrome) of rheumatoid arthritis, including juvenile rheumatoid arthritis, acute rheumatism, lupus erythematosus disseminatus, temporal arteritis (polymyalgia rheumatica).

Skin disorders: Pemphigus vulgaris, bullous pemphigoid, erythrodermas, serious forms of erythema multiforme (Stevens-Johnson syndrome), mycosis fungoides, bullous dermatitis herpetiformis.

Oncological disorders: Lymphatic leukaemia, especially acute forms, malignant lymphoma (Hodgkin’s disease, non-Hodgkin’s lymphoma), metastasized breast cancer, hypercalcaemia as a result of bone metastasis or Kahler’s disease, Kahler’s disease.

Various: Intense allergic reactions; as immunosuppressant in organ transplantation; as an adjuvant in the prevention of nausea and vomiting and in the treatment of cancer with oncolytics that have a serious emetic effect.

4.2 Posology and method of administration

In general, glucocorticoid dosage depends on the severity of the condition and response of the patient. Under certain circumstances, for instance in stress and changed clinical picture, extra dosage adjustments may be necessary. If no favourable response is noted within a couple of days, glucocorticoid therapy should be discontinued.

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 ‘Side effects’).

The initial dosage varies from 0.5 – 10 mg a day depending on the disease being treated. In more severe diseases, doses higher than 10 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 Glensoludex 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 2 mg Glensoludex 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 drug is to be stopped after more than a few days of treatment, it should be withdrawn gradually.

The following equivalents facilitate changing to dexamethasone 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.

Raised intracranial pressure: Initial therapy is usually by injection using an intravenous formulation. When maintenance therapy is required, this should be changed to an oral formulation of dexamethasone 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:

2mg Glensoludex soluble tablets should be administered at 11 pm. Blood samples are then taken at 8 am the next morning for plasma cortisol determination.

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 Glensoludex soluble tablets 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.

Method of administration
Glensoludex soluble tablets should be dissolved in water. The soluble tablets should be dissolved in half a small glass of water and the solution drunk immediately after dissolution. A minimum volume of approximately 50 ml of water is sufficient for complete dissolution.

This formulation of Glensoludex is not suitable for subdivision of dose either as tablet or solution. The tablet strength(s) most appropriate for the prescribed dose should therefore be selected. During tapered dose reduction a change to a lower strength tablet may be needed. When a lower dose than 2mg is required, the patient should be prescribed an alternative formulation - such as an oral solution of Glensoludex sodium phosphate in a low strength formulation - to ensure optimal dose titration.

4.3 Contraindications

- Hypersensitivity to dexamethasone or 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.
- Avoid live vaccines in patients receiving immunosuppressive doses (serum antibody response diminished).

In general no contraindications apply in conditions where the use of glucocorticoids may be lifesaving.

4.4 Special warnings and precautions for use

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

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 (see section 4.2).
In post-marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

**Antiinflammatory/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 contraindicated 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 often be atypical, and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

Appropriate antimicrobial therapy should accompany glucocorticoid therapy when necessary e.g. in tuberculosis and viral and fungal infections of the eye. 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 nonimmune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. *If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and 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 gastrointestinal bleeding and therefore corticosteroids should not be used in cerebral malaria.

*Eye disorders*

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.
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.

Adrenal Suppression

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. 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 HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 1mg 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 6mg 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 6mg daily of dexamethasone.
- Patients repeatedly taking doses in the evening.

Intercurrent illness and stress

During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily reintroduced. Patients under stress may require increased doses of corticosteroids prior, during and after the period of stressful situation.

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.

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.

General

In addition to the information given under the other headings, particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent monitoring is necessary:

a. Osteoporosis (post-menopausal females are particularly at risk).
b. Diabetes mellitus (or a family history of diabetes).
c. Previous corticosteroid-induced myopathy.
d. Liver failure.
e. Epilepsy.
f. Peptic ulceration.
g. Migraine
h. Myasthenia gravis.
i. Non-specific ulcerative colitis, diverticulitis or fresh intestinal anastomosis.
j. History of allergy to corticosteroids.
k. Herpes simplex.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Fat embolism has been reported as a possible complication of hypercortisonism.

Large doses of corticosteroids may mask the symptoms of gastrointestinal perforation.

Reports in the literature suggest an apparent association between use of corticosteroids and left-ventricular free-wall rupture after a recent myocardial infarction; therefore, corticosteroids should be used with great caution in these patients.

In rare cases, decrease or withdrawal of orally administered corticosteroids could reveal underlying disease that is accompanied by eosinophilia (e.g. Churg Strauss Syndrome) in patients with asthma.

The results of a randomised, placebo-controlled study suggest an increase in mortality if methylprednisolone therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS). Therefore, treatment of ARDS with corticosteroids should be initiated within the first two weeks of onset of ARDS.

Hypersensitivity

Rare cases of anaphylactoid or hypersensitivity reactions such as glottis oedema, urticaria and bronchospasm have been reported especially with parenteral administration of corticosteroids and in patients with a history
of allergy. Prophylactic measures should be taken especially if the patient has a history of allergic reactions to medicines.

If such an anaphylactoid reaction occurs, the following measures are recommended: immediate slow intravenous injection of 0.1-0.5ml of adrenaline (solution of 1:1000: 0.1-0.5mg adrenaline dependent on body weight), intravenous administration of aminophylline and artificial respiration if necessary.

**Paediatric population**
Corticosteroids cause a dose-dependent inhibition of growth in infancy, childhood, and adolescence, which may be irreversible. On prolonged administration glucocorticoids may accelerate epiphyseal closure. Treatment should be limited to the minimum dose for the shortest period. Therefore, during long-term treatment with Glensoludex 2 mg soluble tablets, its use should be very clearly justified in children and their growth rate should be checked regularly.

**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.

**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.

**Note on doping**
The use of doping tests when taking Glensoludex 2 mg soluble tablets can lead to positive results.

**Excipient Warnings**
This medicinal product contains 14.96 mg sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.
Glensoludex contains Sunset yellow, a colourant agent which can cause allergic reactions.

**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 (e.g. primidone and phenobarbital), ephedrine, rifabutin, carbamazepine and rifampicin may lead to decreased plasma concentrations of dexamethasone and the dose may need to be increased.

Co-treatment with CYP3A inhibitors, such as ketoconazole, ritonavir and erythromycin, including cobicistat-containing products, may lead to increased plasma concentrations of dexamethasone and it is expected to increase the risk of systemic products. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Dexamethasone reduces the plasma concentration of the antiviral drugs indinavir and saquinavir.

Patients taking methotrexate and dexamethasone have an increased risk of haematological toxicity.

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.

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

Aminogluthethimide: 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 have been reported with prednisolone and dexamethasone. Therefore, glucocorticoids should be taken separately from gastrointestinal topicals, antacids or charcoal, with an interval between treatment 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 once the steroids are discontinued. Steroid withdrawal may result in salicylate intoxication.

The desired effects of anti-hypertensives and diuretics are antagonised by corticosteroids.

The hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics, amphotericin B injection, potassium depleting agents, corticosteroids (gluco-mineralo), tetracosactide and carbenoxolone are enhanced. Hypokalaemia predisposes to cardiac arrhythmia especially “torsade de pointes” and increase the toxicity of cardiac glycosides. Hypokalaemia 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.

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.

Influence on diagnostic tests: Glucocorticoids can suppress skin reaction to allergy testing. Corticosteroids may affect the nitroblue tetrazolium test for bacterial infection and produce false-negative results.
Live attenuated vaccines: 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. The desired effects of hypoglycaemic agents are antagonised by corticosteroids since they impair carbohydrate tolerance. Therefore, blood and urine self-monitoring should be reinforced by the patient, in particular at the start of treatment.

Isoniazid: Serum concentrations of isoniazid may be decreased. 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

Since adequate human reproduction studies have not been performed with corticosteroids, Glensoludex should not be used during pregnancy for maternal indications, unless it is clearly necessary. The lowest effective dose needed to maintain adequate disease control should be used.

Patients with preeclampsia or fluid retention require close monitoring.

Dexamethasone crosses the placenta. Placental transfer in considerable: foetal serum concentrations are similar to maternal concentrations.

When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

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. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism. 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.

Lactation

Glucocorticoids are excreted in small amounts in breast milk and may suppress growth, interfere with endogenous corticosteroid production or cause other unwanted effects. 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.

4.7 Effects on ability to drive and use machines

There are some side effects associated with this product that may affect some patients' ability to drive or operate machinery (see section 4.8)
4.8 Undesirable effects

The incidence of anticipated adverse effects, such as the suppression of the hypothalamic-pituitary-adrenal 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 following side effects have been reported; their frequency is unknown

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Increased susceptibility and severity of (latent) infections with suppression of clinical symptoms and signs, opportunistic infections, reactivation of latent tuberculosis, decreased resistance of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Leucocytosis, lymphopaenia, eosinopaenia, polycythaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions including anaphylaxis have been reported, immunosuppression (see also under “Infections and parasitic diseases”)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Suppression of the hypothalamic-pituitary-adrenal axis, development of Cushing's syndrome (typical symptoms: full-moon face, plethora, truncal obesity), hirsutism, secondary adrenocortical and pituitary insufficiency (particularly in times of stress, as trauma, surgery or illness), negative protein and calcium balance</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight gain, increased appetite, sodium and water retention, potassium loss (caution: rhythm disorders), hypokalaemic alkalosis, increased calcium excretion, manifestation of latent diabetes mellitus, impaired carbohydrate tolerance with increased dose requirements of anti diabetic therapy, hypercholesterolemia, hypertriglyceridaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Psychological dependence, depression, insomnia, aggravation of schizophrenia and psychic disturbances ranging from euphoria to frank psychotic manifestations. A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Vertigo, headache, increased intracranial pressure with papilloedema in children (pseudotumour cerebri) usually following discontinuation of treatment; convulsions and aggravation of epilepsy</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Increased intraocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral, fungal and bacterial infections, exophthalmos, worsening of symptoms associated with corneal ulcers Chorioretinopathy (frequency unknown)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Myocardial rupture following recent myocardial infarction, congestive heart failure in susceptible patients</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension, vasculitis, increased atherosclerosis and risk of thrombosis/thromboembolism</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hiccups</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dyspepsia, peptic ulcers with perforation and haemorrhage, candidiasis, acute pancreatitis, oesophageal ulceration, flatulence, abdominal distension, nausea, vomiting. Perfusion of the small and large bowel particularly in patients with inflammatory bowel disease.</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Impaired wound healing, increased sweating, hypertrichosis, thin fragile skin telangiectasia, striae, erythema, steroid acne, petechiae, ecchymosis, allergic dermatitis, urticaria, angioedema, thinning scalp hair, pigment disorders, increased capillary fragility, perioral dermatitis</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Growth suppression in infants, children and adolescents, premature epiphyseal closure, osteoporosis, vertebral and long bone fractures, avascular necrosis, aseptic</td>
</tr>
</tbody>
</table>
necrosis of the femoral and the humeral bones, tendon rupture, proximal myopathy, muscle weakness, loss of muscle mass

Reproductive system and breast disorders
Menstrual irregularity, amenorrhea, impotence

General disorders and administration site conditions
Malaise, abnormal fat deposits, steroid withdrawal syndrome (see section 4.4)

Injury, poisoning and procedural complications
Reduced response to vaccination and skin tests, bruising

Investigations
Increased or decreased motility and number of spermatozoa

Withdrawal symptoms and signs
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4). A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard

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
ATC Code: H02A B02
Pharmacotherapeutic Group: Glucocorticoids

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, intra-uterine growth can be delayed. All these effects were seen at high dosages.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Bicarbonate
Disodium Citrate 1.5Hydrate
Povidone K30
Sodium Saccharin
Sodium Benzoate
Yellow Sunset (E110)

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

6.3 Shelf life

3 years

6.4 Special precautions for storage
This medicinal product does not require any special temperature storage conditions.
Store in the original package.

6.5 Nature and contents of container
Alu-alu blisters foil blisters packed in cartons containing 10, 30, 50 or 100 tablets.
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
Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue
Kenton, Middlesex
HA3 0BU
United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 25258/0161

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
14/09/2015

10 DATE OF REVISION OF THE TEXT
26/06/2017