IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0535/005/003
Case No: 2026443

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Shire Pharmaceuticals Limited

Hampshire International Business Park, **Chineham**, **Basingstoke, Hampshire RG24 8EP**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Calcort 30mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **14/08/2007**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calcort 30 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Deflazacort 30 mg.

Excipients: also includes lactose monohydrate 313 mg per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Round white tablet, marked with a cross on one face and '30' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

A wide range of conditions may sometimes need treatment with glucocorticoids. The indications include:

Primary and secondary adrenocortical insufficiency, rheumatic disorders, collagen diseases, pulmonary diseases, allergic conditions, haematological diseases, neoplastic diseases, dermatological diseases, renal diseases, gastrointestinal diseases, ophthalmic diseases and nervous system disorders.

4.2 Posology and method of administration

Route of Administration: Oral

Recommended Dosage:

Dosage may range up to 90 mg daily although higher doses can be administered. Doses should be individually titrated according to diagnosis, severity of disease, prognosis, probable duration of disease or therapy, and patient response and tolerance. The lowest dose that will produce an acceptable result should be used; when it is possible to reduce the dosage, this must be accomplished gradually. During prolonged therapy, dosage may need to be increased temporarily during periods of stress or in exacerbation of illness.

ADULTS

Acute Disorders:
Up to 90mg daily, depending on severity of symptoms, for a few days.

Depending on clinical response, dose should be gradually decreased by increments to the lowest effective dose.

Chronic Disorders:
Such as rheumatoid arthritis: maintenance doses are usually 3 - 18mg/day.

Hepatic Impairment:
In patients with hepatic impairment, blood levels of deflazacort may be increased. Therefore the dose of deflazacort should be carefully monitored and adjusted to the minimum effective dose.

Renal Impairment:
In renally impaired patients, no special precautions other than those usually adopted in patients receiving glucocorticoid therapy are necessary.

Elderly:
In elderly patients, no special precautions other than those usually adopted in patients receiving glucocorticoid therapy are necessary. The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age (see Warnings and Precautions).

Children:
There has been limited exposure of children to deflazacort in clinical trials.
In children, the indications for glucocorticoids are the same as for adults, but it is important that the lowest effective dosage is used. Alternate day administration may be appropriate (see Warnings and Precautions). Doses of deflazacort usually lie in the range 0.25 – 1.5 mg/kg/day.

4.3 Contraindications

Systemic infections unless specific anti-infective therapy is employed. Hypersensitivity to deflazacort or any of the ingredients. Patients receiving live virus immunisation.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.

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

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 alternate days.

Frequent patient review is required to appropriately titrate the dose against disease activity (see Dosage section).

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. During prolonged therapy, any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy, they may need to be temporarily re-introduced.

Anti-inflammatory/immunosuppressive effects and infection
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.

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 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.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Immunisation procedures should not be undertaken with patients on glucocorticoids, especially on high doses, because of the possibility of dissemination of live vaccines and/or failure of antibody response.

Prolonged use of glucocorticoids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Use in active tuberculosis should be restricted to those cases of fulminating and disseminated tuberculosis in which deflazocort is used the management with appropriate antituberculosis regimen.
If glucocorticoids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged glucocorticoid therapy, these patients should receive chemoprophylaxis.

The following clinical conditions require special caution and frequent patient monitoring is necessary:

- Cardiac disease or congestive heart failure, hypertension, thromboembolic disorders. Glucocorticoids can cause salt and water retention, and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary.
- Gastritis or oesophagitis, diverticulitis, ulcerative colitis if there is probability of impending perforation, abscess or pyogenic infections, fresh intestinal anastomosis, active or latent peptic ulcer.
- Diabetes mellitus or a family history, osteoporosis, myasthenia gravis, renal insufficiency.
- Emotional instability or psychotic tendency, epilepsy.
- Previous corticosteroid-induced myopathy.
- Liver failure/cirrhosis.
- Renal insufficiency.
- Hypothyroidism.
- Ocular herpes simplex because of possible corneal perforation.

Use in Children:
Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence which may be irreversible.

Use in the Elderly:
The common adverse effects of 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.

Since complications of glucocorticoid therapy are dependent on dose and duration of therapy, the lowest possible dose must be given and a risk/benefit decision must be made as to whether intermittent therapy should be used.

4.5 Interaction with other medicinal products and other forms of interaction

The same precautions should be exercised as for other glucocorticoids. Deflazacort is metabolised in the liver. It is recommended to increase the maintenance dose of deflazacort if drugs which are liver enzyme inducers are co-administered, e.g. rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone and aminoglutethimide. For drugs which inhibit liver enzymes, e.g. ketoconazole it may be possible to reduce the maintenance dose of deflazacort.

In patients taking estrogens, corticosteroid requirements may be reduced.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

In patients treated with systemic corticosteroids, use of non-depolarising muscle relaxants can result in prolonged relaxation and acute myopathy. Risk factors for this include prolonged and high dose corticosteroids treatment, and prolonged ventilation (such as in the ITU setting).

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

As glucocorticoids can suppress the normal responses of the body to attack by micro-organisms, it is important to ensure that any anti-infective therapy is effective and it is recommended to monitor patients closely.

Concurrent use of glucocorticoids and oral contraceptives should be closely monitored as plasma levels of glucocorticoids may be increased. This effect may be due to a change in metabolism or binding to serum proteins. Antacids may reduce bioavailability; leave at least 2 hours between administration of deflazacort and antacids.

4.6 Pregnancy and lactation

Human reproduction studies have not been performed with glucocorticoids, but they are known to be teratogenic in animals. Deflazacort was shown to have dose dependent teratogenic effects in rats and rabbits.

Intra-uterine growth retardation in the foetus and a small increased risk of cleft palate have been reported with corticosteroids. Hypoadrenalism may occur in the neonate.

Use during pregnancy or during lactation is not recommended and should only be considered when potential benefit outweighs potential risk. Infants born to mothers receiving glucocorticoids during pregnancy should be carefully observed for signs of hypoadrenalism. Glucocorticoids are excreted in mother's milk and can cause growth suppression and hypoadrenalism in breast fed infants; therefore mothers taking glucocorticoids should be advised not to breast feed.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile and reported adverse events, it is unlikely that deflazacort will produce an effect on the ability to drive and use machines.

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see Warnings and Precautions).

Endocrine/metabolic
Suppression of the hypothalamic-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea. Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy, negative protein and calcium balance. Increased appetite.

Anti-inflammatory and immunosuppressive effects
Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see Warnings and Precautions).

Musculoskeletal
Osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture. Muscle wasting or myopathy (acute myopathy may be precipitated by non-depolarising muscle relaxants - see section 4.5), negative nitrogen balance.

Fluid and electrolyte disturbance
Sodium and water retention with hypertension, oedema and heart failure, potassium loss, hypokalaemic alkalosis.

Neuropsychiatric
Headache, vertigo, euphoria, psychological dependence, hypomania or depression, insomnia, restlessness and aggravation of schizophrenia. Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy.

Ophthalmic
Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts especially in children, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.

Gastrointestinal
Dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis (especially in children), candidiasis, nausea.

Dermatological
Impaired healing, skin atrophy, bruising, telangiectasia, striae, acne.

General
Hypersensitivity including anaphylaxis has been reported. Leucocytosis. Thromboembolism. Rare incidence of benign intracranial hypertension.

Withdrawal symptoms and signs
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see Warnings and Precautions).

A ‘withdrawal syndrome’ may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight. This may occur in patients even without evidence of adrenal insufficiency.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

4.9 Overdose

It is unlikely that treatment is needed in cases of acute overdosage. The LD_{50} for the oral dose is greater than 4000mg/kg in laboratory animals.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Deflazacort is a glucocorticoid. Its anti-inflammatory and immunosuppressive effects are used in treating a variety of diseases and are comparable to other anti-inflammatory steroids. Clinical studies have indicated that the average potency ratio of deflazacort to prednisone is 0.64 – 0.89.

5.2 Pharmacokinetic properties

Orally administered deflazacort appears to be well absorbed and is immediately converted by plasma esterases to the pharmacologically active metabolite (D 21-OH) which achieves peak plasma concentrations in 1.5 to 2 hours. It is 40% protein-bound and has no affinity for corticosteroid-binding-globulin (transcortin). Its elimination plasma half-life is 1.1 to 1.9 hours. Elimination takes place primarily through the kidneys; 70% of the administered dose is excreted in the urine. The remaining 30% is eliminated in the faeces. Metabolism of D 21-OH is extensive; only 18% of urinary excretion represents D 21-OH. The metabolite of D 21-OH, deflazacort 6-beta-OH, represents one-third of the urinary elimination.

5.3 Preclinical safety data

Safety studies have been carried out in the rat, dog, mouse and monkey. The findings are consistent with other glucocorticoids at comparable doses.

Teratogenic effects demonstrated in rodents and rabbits are typical of those caused by other glucocorticoids. Deflazacort was not found to be carcinogenic in the mouse, but studies in the rat produced carcinogenic findings consistent with the findings with other glucocorticoids.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Lactose Monohydrate
Maize Starch
Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

5 years

6.4 Special precautions for storage

Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container

Deflazacort will be packed in blister packs of polyvinylchloride and aluminium foil presented in cardboard boxes.

Each pack contains 30 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Limited,
Hampshire International Business Park,
Chineham,
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8 MARKETING AUTHORISATION NUMBER

PA 535/5/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th August 1992

Date of last renewal: 14th August 2007

10 DATE OF REVISION OF THE TEXT

October 2007