1.6 PRODUCT INFORMATION

1.6.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

DYNACORT-30 mg TABLETS

Active Ingredient(s) (INN or Scientific name): Deflazacort

Dosage Form and sub-form: TABLETS

Strength: 30 mg

Route of Administration: Oral

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Uncoated Tablets Contains

Deflazacort 30 mg

Excipients Q.S

Batch Size: 0.35 Lac Tablets

Ingredients	**Specification**	**Unit Qty in Mg**	**Qty in mg Kg**	**Category**
Deflazacort $	IH	30.00	1.05	Active
Lactose Monohydrate #	BP	150	5.25	Diluents
Maize Starch *	BP	30.486	1.067	Diluents
Microcrystalline cellulose**	BP	49.486	1.732	Disintegrating agent
Maize Starch	BP	5.00	0.175	Binder
Purified water	USP	22.857	0.80	Vehicle
Microcrystalline cellulose pH102	BP	20.00	0.70	Disintegrating agent
Magnesium Stearate	BP	3.00	0.105	Lubricant

$ Quantity of API is calculated on 100 % assay basis to be dispensed on the basis of as is potency.

Difference in the quantity of API is adjusted with the quantity of Lactose to maintain batch weight.

* 5 % & ** 3 % excess to compensate loss on drying.

Abbreviation: BP: British Pharmacopoeia, USP- United State Pharmacopoeia, IH: In House Specification

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Anaphylaxis, asthma, severe hypersensitivity reactions
- Rheumatoid arthritis, juvenile chronic arthritis, polymyalgia rheumatica
- Systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease (other than systemic sclerosis), polyarteritis nodosa, sarcoidosis
- Pemphigus, bullous pemphigoid, pyoderma gangrenosum
- Minimal change nephrotic syndrome, acute interstitial nephritis
- Rheumatic carditis
- Ulcerative colitis, Crohn's disease
- Uveitis, optic neuritis
- Autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura
- Acute and lymphatic leukaemia, malignant lymphoma, multiple myeloma
- Immune suppression in transplantation

4.2 Posology and method of administration

Deflazacort is a glucocorticoid derived from prednisolone and 6 mg of deflazacort has approximately the same anti-inflammatory potency as 5mg prednisolone or prednisone.

Doses vary widely in different diseases and different patients. In more serious and life-threatening conditions, high doses of deflazacort may need to be given. When deflazacort is used long term in relatively benign chronic diseases, the maintenance dose should be kept as low as possible. Dosage may need to be increased during periods of stress or in exacerbation of illness.

The dosage should be individually titrated according to diagnosis, severity of disease and patient response and tolerance. The lowest dose that will produce an acceptable response should be used.

Adults

For acute disorders, up to 120 mg/day deflazacort may need to be given initially. Maintenance doses in most conditions are within the range 3 - 18 mg/day. The following regimens are for guidance only.

Rheumatoid arthritis: The maintenance dose is usually within the range 3 - 18 mg/day. The smallest effective dose should be used and increased if necessary.

Bronchial asthma: In the treatment of an acute attack, high doses of 48-72 mg/day may be needed depending on severity and gradually reduced once the attack has been controlled. For maintenance in chronic asthma, doses should be titrated to the lowest dose that controls symptoms.

Other conditions: The dose of deflazacort depends on clinical need titrated to the lowest effective dose for maintenance. Starting doses may be estimated on the basis of ratio of 5mg prednisone or prednisolone to 6mg deflazacort.

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.

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.

Doses of deflazacort usually lie in the range 0.25 - 1.5 mg/kg/day. The following ranges provide general guidance:

Juvenile chronic arthritis: The usual maintenance dose is between 0.25 - 1.0 mg/kg/day.

Nephrotic syndrome: Initial dose of usually 1.5 mg/kg/day followed by down titration according to clinical need.

Bronchial asthma: On the basis of the potency ratio, the initial dose should be between 0.25 - 1.0 mg/kg deflazacort on alternate days.

4.3 Method of administration

Oral Administration

4.4 Contraindications

Hypersensitivity to the active substance or to any of the Excipients.

Systemic infection unless specific anti-infective therapy is employed.

Patients receiving live virus immunisation.

4.5 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose 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.

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 which could be fatal, 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.

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.

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 chicken

pox 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.

Live vaccines should not be given to individuals with impaired responsiveness. The antibody response to other vaccines may be diminished.

Systemic glucocorticoid treatment can cause chorioretinopathy which can lead to visual disorders including visual loss. Prolonged use of systemic glucocorticoid treatment even at low dose can cause chorioretinopathy.

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 deflazacort is used for 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.

Tendonitis and tendon rupture are known class effect of glucocorticoids. The risk of such reactions may be increased by coadministration of quinolones.

Special precautions

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

• Cardiac disease or congestive heart failure (except in the presence of active rheumatic carditis), 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.
• Hypothyroidism and cirrhosis, which may increase glucocorticoid effect.
• Ocular herpes simplex because of possible corneal perforation.

Glucocorticoids are known to cause irregular menstruation and leukocytosis, care should be taken with deflazacort.

4.6 Paediatric population

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

4.7 Interaction with other medicinal products and other forms of interaction

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, beta 2-agonists, xanthines 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 corticosteroid treatment, and prolonged duration of muscle paralysis. This interaction is more likely following 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.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. 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.

4.8 Additional information on special populations

Elderly Use

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.

4.10 Pregnancy and Lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs, however, deflazacort does cross the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine 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. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Nursing Mothers

Corticosteroids are excreted in breast milk, although no data are available for deflazacort. Doses of up to 50 mg daily of deflazacort are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression but the benefits of breast feeding are likely to outweigh any theoretical risk.

4.11 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.

4.12 Undesirable effects

Common: Weight gain.

Uncommon: impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy, sodium and water retention with hypertension, potassium loss and hypokalaemic alkalosis when coadministered with beta 2-agonist and xanthines.

Not known: Negative protein and calcium balance, increased appetite.

Infections and Infestations

Uncommon: Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis.

Not known: candidiasis.

Musculoskeletal and connective tissue disorders

Uncommon: Osteoporosis, vertebral and long bone fractures.

Rare: Muscle wasting

Not known: avascular osteonecrosis, tendonitis and tendon rupture when coadministered with quinolones, myopathy (acute myopathy may be precipitated by non-depolarising muscle relaxants, negative nitrogen balance.

Reproductive system and breast disorders

Not known: Menstrual irregularity

Cardiac disorders

Not known: Heart failure

Nervous system disorders

Uncommon: Headache, vertigo.

Not known: restlessness, Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal, aggravation of epilepsy.

Psychiatric disorders

A wide range of psychiatric reactions including affective disorders such as:

Uncommon: depressed and labile mood.

Not known: irritable, euphoric, suicidal thoughts.

Psychotic reactions including:

Not known: mania, delusions, hallucinations, aggravation of schizophrenia

Other reactions including:

Uncommon: behavioural disturbances

Not known: 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.

Eye disorders

Not known: Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts especially in children, chorioretinopathy, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.

Gastrointestinal disorders

Uncommon: Dyspepsia, peptic ulceration, haemorrhage, nausea.

Not known: perforation of peptic ulcer, acute pancreatitis (especially in children), candidiasis.

Skin and subcutaneous tissue disorders

Uncommon: hirsutism, striae, acne,

Rare: bruising

Not known: Skin atrophy, telangiectasia.

General disorders and administration site conditions

Uncommon: Oedema.

Not known: impaired healing.

Immune system disorders

Uncommon: Hypersensitivity including anaphylaxis has been reported.

Blood and lymphatic system disorders

Not known: Leukocytosis

Vascular disorders

Not known: Thromboembolism in particular in patients with underlying conditions associated with increased thrombotic tendency, rare incidence of benign intracranial hypertension

4.13 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoid for systemic use

ATC code: H02AB13

Mechanism of action

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 prednisolone is 0.69-0.89.

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

Lactose Monohydrate BP

Maize Starch BP

Microcrystalline cellulose BP

Microcrystalline cellulose BP pH102

Magnesium Stearate BP

6.2 Incompatibilities

None known

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in a cool & dry place below 30°C. Protect from light.

6.5 Nature and contents of container

3 Blister of 10 tablets packed in cartons along with Product insert. (3×10's Alu-Alu Blisters pack)

7. MARKETING AUTHORISATION HOLDER

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