SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Precortisyl Forte Tablets 25mg
Prednisolone 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prednisolone EP 25.0mg

3 PHARMACEUTICAL FORM

Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Collagen Diseases:-

Systemic Lupus Erythematous, Acute Rheumatic Fever

Haematological Disorders:-

Acute granulocytic Leukaemia, Acute Monocytic Leukaemia, Chronic Lymphocytic Leukaemia, Thromcytopenia, Haemolytic Anaemia.

Miscellaneous:-

Ulcerative Colitis

Pemphigus
Nephrosis

4.2 Posology and method of administration

Route of Administration: Oral.

In the initial treatment of acute illnesses such as described under 'Therapeutic Indications', daily doses of 75mg or more may be needed. The daily dose should be taken in the morning after breakfast.

In alternate day therapy, the average daily dose is doubled and given every other day in the morning after breakfast.

For further information with reference to dosage see 'Special Warnings and Special Precautions for Use'.

4.3 Contraindications

Systemic fungal and viral infections: acute bacterial infections unless specific anti-infective therapy is given.

Hypersensitivity to any ingredient.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.

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

Care and frequent patient monitoring is necessary in patients with the following:

- diabetes mellitus (or a family history of diabetes),
- osteoporosis (post-menopausal women are particularly at risk),
- hypertension,
- congestive heart failure,
- myasthenia gravis, myopathy, muscle mass wasting and loss

- patients with a history of severe or pre-existing affective disorders (especially a history of steroid psychosis),
- glaucoma or a family history of glaucoma,
- epilepsy
- liver failure
- renal insufficiency
- peptic ulceration
- Non-specific ulcerative colitis

Infections
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.

Chicken pox
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.

Tuberculosis
Corticosteroids should be given with care in patients with a history of tuberculosis or the characteristic appearance of tuberculosis disease on X-Ray. The emergence of tuberculosis can however, be prevented by the prophylactic use of anti-tuberculosis therapy.

Live virus vaccines
Should not be administered to patients with impaired immune-responsiveness. If in activated vaccines are administered to such individuals, the expected serum antibody response may not be obtained.

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 temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

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.

Potentially severe 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) 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 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 maniac-depressive illness and previous steroid psychosis.

Visual disturbances

May be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Pheochromocytoma crisis,

Pheochromocytoma crisis, which can be fatal, has been reported after administration of corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation. (see section 4.8).

Hypertrophic cardiomyopathy

Has been reported after systemic administration of glucocorticosteroids in preterm infants. In infants receiving administration of systemic glucocorticosteroids, echocardiograms should be performed to monitor myocardial structure and function.

Scleroderma renal crisis*

Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

Special populations

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

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.

Withdrawal
In patients who have received more than physiological doses of systemic corticosteroids (approximately 7.5mg prednisolone or equivalent) 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 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 equivalent to 7.5mg of prednisolone is reached, dose reduction should be slower to allow 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 40mg daily prednisolone, or equivalent for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patients 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.
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 40mg daily of prednisolone or equivalent
- Patients repeatedly taking doses in the evening.

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. A ‘withdrawal syndrome’ may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

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

4.5 Interaction with other medicinal products and other forms of interaction

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.

Rifampicin, rifabutin, carbamazepine, phenobarbital and other barbiturates, phenytoin, phenyl butazone, primidone and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

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

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

In patients treated with systemic corticosteroids, use of non-depolarizing muscle relaxants can result in prolonged relaxation and acute myopathy. Risk factors for this include prolonged and high dose corticosteroids treatment and prolonged duration of muscle paralysis. This interaction is more likely to occur following prolonged ventililation (such as in an ITU setting).

Corticosteroid requirements may be reduced in patients taking estrogens (e.g. contraceptive products)

4.6 Pregnancy and lactation

Pregnancy: The ability of corticosteroids to cross the placenta varies between individual drugs, however, 88% of prednisolone is inactivated as it crosses the placenta. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids cause 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 intrauterine growth retardation. Hypoadrenalism may occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously after birth and is rarely clinically important. As with all other drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with abnormal pregnancies may be treated as though they were in a non-gravid state.

Lactation: Corticosteroids are excreted in small amounts in breast milk, however, doses of up to 40mg daily of prednisolone 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 theoretic risk.

4.7 Effects on ability to drive and use machines

Not applicable.

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 duration of treatment (see section 4.4).

Blood and metabolic disorders

- Leukcytosis (sometimes an almost leukaemoid-like reaction) may occur.
- Thromboembolism
- Hypertension

Endocrine and metabolic disorders

- Suspension of growth in infancy, childhood and adolescence,
- Menstrual irregularities, amenorrhoea,
- Cushingoid facies,
- Hirsutism and weight gain, increased appetite,
- Decreased carbohydrate tolerance with development of classical symptoms of diabetes mellitus, increased need for insulin or oral hypoglycaemic agents in diabetes, Negative nitrogen balance due to protein catabolism and negative calcium balance.
- Pheochromocytoma crisis.
- Potassium loss and hypokalaemic alkalosis.
- Fluid and electrolyte disturbance: sodium and water retention leading to congestive heart failure in susceptible subjects,

Immune system disorders

- Hypersensitivity including anaphylaxis
- 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 tuberculous may be masked and may reach an advanced stage before being recognised.

Gastro-intestinal disorders

- Peptic ulceration with perforation and haemorrhage. Fatalities have been reported: perforation of the small and large bowel, particularly in patients with inflammatory bowel disease; dyspepsia,
- Abdominal distension
- Oesophageal ulceration
- Candidiasis
- Acute pancreatitis

Musculoskeletal and connective tissue disorders
- Muscle weakness,
- Proximal myopathy,
- wasting and loss of muscle mass,
- Osteoporosis,
- Avascular necrosis of bone,
- Pathological fractures of long bones and rupture of tendons.
- Acute myopathy may be precipitated in patients administered non-depolarising muscle relaxants (see section 4.5).
- Vertebral fractures and fractures of the long bones (frequency not known)

Skin and subcutaneous tissue disorders
- Hypertrichosis,
- Purpura,
- Impaired wound healing,
- Skin atrophy,
- Petechial haemorrhage and ecchymoses,
- Erythema,
- Telangiectasia,
- Skin striae
- Acne

Psychiatric disorders

a) Potentially severe Psychiatric reactions:

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, restlessness, 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.

b) Other psychiatric reactions:

There is increased risk of raised intracranial pressure and papilloedema in children (pseudotumour cerebri) usually after treatment withdrawal. Aggravation of epilepsy. Psychological dependence may be marked.

Eye disorders

- Increased intra-ocular pressure with development of glaucoma,
- Papilloedema,
- Posterior subcapsular cataracts,
- Vision blurred (see also section 4.4)
- Corneal and scleral thinning or perforation after prolonged use.
- Viral or fungal ophthalmic disease may be reignited or spread.
- Chorioretinopathy.

Cardiac disorders
Hypertrophic cardiomyopathy in preterm infants.
Frequency not known: Bradycardia *
*Following high doses

Renal and urinary disorders
Frequency not known: Scleroderma renal crisis (see section 4.4).
Amongst the different subpopulations the occurrence of scleroderma renal crisis varies. The highest risk has been reported in patients with diffuse systemic sclerosis. The lowest risk has been reported in patients with limited systemic sclerosis (2%) and juvenile onset systemic sclerosis (1%).

Infections and infestations
Opportunistic infections occur more frequently in corticosteroid recipients
Clinical reactivation of previously dormant tuberculosis,

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of an overdose, supportive and symptomatic therapy is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Prednisolone is a well absorbed glucocorticoid that exists in a metabolically active form.

5.2 Pharmacokinetic properties

Prednisolone is readily absorbed from gastro-intestinal tract. Peak plasma concentration is obtained 1-2 hours after oral administration and it had a plasma half-life of 2-3 hours.

It is excreted in the urine as free and conjugated metabolites together with an appreciable proportion of unchanged prednisolone.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, Potato Starch, Pregelatinised Maize Starch, Magnesium Stearate, Talc (purified).

6.2 Incompatibilities

None known.

6.3 Shelf life

Glass Bottle: 60 months.

Blister Pack: 36 months.

6.4 Special precautions for storage

Glass Bottle: Protect from light.

Blister Pack: Protect from light. Store below 25°C in a dry place.

6.5 Nature and contents of container

Glass Bottles of 28, *56*, 84, 100 tablets.
(Amber PH EUR type III glass, bottle with low density polythene pilfer proof J. caps.
Cotton wool is used to occupy space in the container).

Blister packs of 28, 56, 84 tablets
(Opaque PVC blisters / aluminium foil).

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

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