SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prednisolone Tablets BP 5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Prednisolone 5 mg

For excipients see 6.1

3. PHARMACEUTICAL FORM

Tablet

White, circular flat bevelled edged tablets with breakline.

4. Clinical Particulars

4.1. Therapeutic Indications

In the management of corticosteroid sensitive dermatoses, rheumatic and collagen disorders, asthma including status asthmaticus, pulmonary fibrosis, adrenal hyperplasia, thrombocytopenic purpura and other haemaopoietic dysplasias, gastrointestinal disorders, irido-choroditis.

4.2 Posology and method of administration

Route of administration – Oral
A high initial dose is often given to achieve disease control, followed by a lower maintenance dose; however, in some cases short treatment courses are all that is required. The risk of side effects increases with dose and duration of corticosteroid therapy and so the dose of prednisolone should be the minimum required to achieve and maintain disease control. Individual doses should be determined and re-evaluated regularly according to disease activity. Doses should preferably be taken in the morning after breakfast to limit the steroid-induced suppression of cortisol secretion, alternate-day administration may be possible in some cases and has the benefit of further reducing pituitary-adrenal suppression.

Adults: An initial dose of 10-20mg daily (up to 60mg in severe disease) is given to achieve disease control, this is followed by a gradual reduction to a maintenance dose of 2.5-15mg daily (higher doses may be required in some cases)

Children: Prednisolone should be used only when indicated, at the lowest dose and for the shortest time possible to achieve the desired effect (see section 4.4)

Elderly: Treatment of elderly patients, particularly if long-term, should take into consideration the more serious consequences of the common side effects of corticosteroids in old age (see section 4.4).

Treatment 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 carriedout depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about hypothalamic-pituitary-adrenal (HPA) suppression, the dose of 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 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 40mg daily of prednisolone, or equivalent 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 40mg daily of prednisolone (or equivalent).
- Patients repeatedly taking doses in the evening.

During prolonged therapy, dosage may need to be temporarily increased during periods of stress or during exacerbations of the disease

4.3 Contraindications

Systemic infection unless specific anti-infective therapy is employed.

Use in patients hypersensitive to any ingredient.

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

Patients with ocular herpes simplex due to the possibility of perforation.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.
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 section 4.2).

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

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 of weeks of stating 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 or 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, previous steroid psychosis, emotional instability or psychotic tendencies.

Caution is necessary when oral corticosteroids, including prednisolone, are prescribed in patients with the following conditions, and frequent patient monitoring is necessary.

- Tuberculosis: Those with a previous history of, or X-ray changes characteristic of, tuberculosis. The emergence of active tuberculosis can however be prevented by the prophylactic use of anti-tuberculosis therapy.
- Hypertension.
- Congestive heart failure.
- Liver failure. Corticosteroid effects may be enhanced in those with chronic liver disease and those with impairment of hepatic function
- Renal insufficiency.
- Diabetes mellitus or in those with a family history of diabetes.
- Osteoporosis: This is of special importance in post-menopausal females who are at particular risk.
- Epilepsy, and/or seizure disorders
- Peptic ulceration.
- Previous steroid myopathy.
- Glucocorticoids should be used cautiously in patients with myasthenia gravis receiving anticholinesterase therapy.
- Because cortisone has been reported rarely to increase blood coagulability and to precipitate intravascular thrombosis, thromboembolism, and thrombophlebitis, corticosteroids should be used with caution in patients with thromboembolic disorders.
- Duchenne's muscular dystrophy: transient rhabdomyolysis and myoglobinuria may occur following strenuous physical activity. It is not known whether this is due to prednisolone itself or the increased physical activity.
- Corticosteroid effects may be enhanced in patients with hypothyroidism
- Corticosteroids may activate amoebiasis or strongyloidiasis and should be excluded before initiating treatment in those at risk or with suggestive symptoms.
- An anaesthetist should be aware that the patient is taking or has been taking a corticosteroid to avoid a precipitous fall in blood pressure during anaesthesia or in the following postoperative period.
- Glaucoma or in those with a family history of glaucoma.
- Recent myocardial infarction (rupture)
- Patients with a history of severe affective disorders and particularly those with a previous history of corticosteroid induced psychosis

Adrenocortical Insufficiency Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy.

Acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage (see below for advice on appropriate withdrawal of steroids). This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineral corticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. 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 when corticosteroids including prednisolone are used. The immunosuppressive effects of glucocorticoids may result in activation of latent infection or exacerbation of intercurrent infections.

Chickenpox 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.

Measles 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.

Administration of Live Vaccines Live vaccines should not be given to individuals on high doses of corticosteroids, due to impaired immune response. Live vaccines should be postponed until at least 3 months after stopping corticosteroid therapy. (See sections 4.3 and 4.5).

Ocular Effects Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible perforation.

Cushing's disease Because glucocorticoids can produce or aggravate *Cushing's syndrome*, glucocorticoids should be avoided in patients with Cushing's disease.

Use in children Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible and therefore long-term administration of pharmacological doses should be avoided. The growth and development of infants and children should be closely monitored during treatment. Treatment should be administered where possible as a single dose on alternate days

Use in the 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, especially osteoporosis, diabetes, hypertension, hypokalaemia, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

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

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 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 equivalent to 7.5mg of prednisolone 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 40mg daily of prednisolone, or equivalent 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 40mg daily of prednisolone,
• Patients repeatedly taking doses in the evening.
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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medications on prednisolone

Antacids can reduce the absorption of prednisolone if given in high doses. Indigestion remedies should not be taken at the same time of day as prednisolone.

Hepatic microsomal enzyme inducers Drugs that induce hepatic enzyme cytochrome P-450 (CYP) isoenzyme 3A4 such as phenobarbital, phenytoin, rifampicin, rifabutin, carbamazepine, primidone and aminoglutethimide may reduce the therapeutic efficacy of corticosteroids by increasing their rate of metabolism. Lack of expected response may be observed and the dose of prednisolone may need to be increased.

Hepatic microsomal enzyme inhibitors Drugs that inhibit hepatic enzyme cytochrome P-450 (CYP) isoenzyme 3A4 such as itraconazole and possibly ketoconazole and erythromycin may decrease glucocorticoid clearance. Dosages of glucocorticoids given in combination with such drugs may need to be decreased to avoid potential adverse effects.

Antibacterials Rifamycins accelerate metabolism of corticosteroids and thus may reduce their effect. Erythromycin inhibits metabolism of methylprednisolone and possibly other corticosteroids.

Antiepileptics Carbamazepine, phenobarbital, phenytoin, and primidone accelerate metabolism of corticosteroids and may reduce their effect.

Ritonavir Ritonavir possibly increases plasma concentrations of prednisolone and other corticosteroids.

Ciclosporin Concomitant administration of prednisolone and ciclosporin may result in decreased plasma clearance of prednisolone (i.e. increased plasma concentration of prednisolone). The need for appropriate dosage adjustment should be considered when these drugs are administered concomitantly.

Mifepristone The effect of corticosteroids may be reduced for 3-4 days after the administration of mifepristone.

Oestrogens and progestogens Oestrogens and progestogens may potentiate the effects of glucocorticoids and dosage adjustments may be required if oestrogens and progestogens are added to or withdrawn from a stable dosage regimen.

Carbimazole enhances the metabolism of corticosteroids and its therapeutic effects may be reduced. Therefore it may be necessary to adjust the dose of prednisolone accordingly.

Effect of prednisolone on other medications

- Aspirin should be used cautiously in conjunction with glucocorticoids in patients with hypoprothrombinaemia. Concurrent use of aspirin and prednisolone may result in an increased risk of gastrointestinal ulceration and sub□therapeutic aspirin serum concentrations.
- Etoposide metabolism may be inhibited by corticosteroids in vitro. This may lead to an increase in both efficacy and toxicity of the etoposide. Monitoring would be prudent.
- Corticosteroids should not be used concurrently with retinoids and tetracyclines due to increased intracranial pressure.
- The hypokalaemic effects of carbenoxolone are enhanced

Neuromuscular blockers Corticosteroids possibly antagonise the effects of pancuronium and vercuronium. This may occur in patients taking corticosteroids long term and may be expected with all competitive neuromuscular blockers.

Diuretics Corticosteroids antagonise the effects of diuretics and may enhance the hypokalaemic effects of acetazolamide, loop and thiazide diuretics.

Antihypertensive agents Corticosteroids antagonise the desired hypotensive effect of antihypertensive drugs

Somatropin The growth promoting effect of somatropin may be inhibited by prednisolone.

Antidiabetic agents Glucocorticoids may increase blood glucose levels. Patients with diabetes mellitus receiving insulin and/or oral hypoglycemic agents may require dosage adjustments of their antidiabetic therapy.

Non-steroidal anti-inflammatory drugs The incidence of gastrointestinal bleeding and ulceration may be increased when corticosteroids are taken with NSAIDS. The

renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.
NSAIDs such as indometacin may increase the risk of GI ulceration. The possiblity of GI ulceration should be considered with concomitant use with any other NSAIDs.

Anticoagulants Response to anticoagulants may be reduced or, less often, enhanced by corticosteroids. Close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Amphotericin There is an increased risk of hypokalaemia when corticosteroids are given with amphotericin, therefore concomitant use should be avoided unless corticosteroids are required to control reactions.

Cardiac Glycosides Corticosteroid-induced hypokalaemia increases the risk of toxicity associated with cardiac glycosides.

Methotrexate Prednisolone may decrease methotrexate clearance increasing the risk of methotrexate toxicity.

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

Sympathomimetics There is an increased risk of hypokalaemia if high doses of corticosteroids given with high doses of bambuterol, fenoteral, formoteral, ritodrine, salbutamol, salmeterol and terbutaline.

Theophylline There is an increased risk of hypokalaemia when corticosteroids are given with theophylline.

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 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. Cataracts have also been rarely reported. As with all drugs, corticosteroids should be prescribed only when the benefits to 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.

Patients with pre□eclampsia or fluid retention require close monitoring.

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 theoretical risk.

4.7 Effects on ability to drive and use machines

If insufficient sleep occurs, the likelihood of impaired alertness may be increased; patients should make sure they are not affected before driving or operating machinery.

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 "other special warnings and precautions"). 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.

Anti-inflammatory/immunosuppressive: Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis. See "other special warnings and precautions".

Gastrointestinal: Abdominal distension, acute pancreatitis, dyspepsia, nausea, increased appetite, oesophageal candidiasis, oesophageal ulceration, peptic ulceration with perforation and haemorrhage, perforation of the small bowel, particularly in patients with inflammatory bowel disease.

Endocrine/metabolic: Cushingoid facies, growth suppression in infancy, childhood and adolescence, hirsutism, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, menstrual irregularity and amenorrhoea, negative protein and calcium balance, suppression of the hypothalamo-pituitary adrenal axis, and weight gain. Although the frequency is not known, there is a risk for Cushing Syndrome.

Fluid and electrolyte disturbance: Hypertension, nocturia, hypokalaemic alkalosis, potassium loss, sodium and water retention, risk of congestive heart failure in susceptible patients.

Musculoskeletal: Avascular osteonecrosis, osteoporosis, proximal myopathy, tendon rupture, vertebral and long bone fractures, muscle weakness, wasting and loss of muscle mass.

Dermatological: Acne, bruising, impaired healing, skin atrophy, striae, telangiectasia.

Neuropsychiatric: 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), marked euphoria leading to dependence; aggravation of epilepsy, behavioural disturbances, irritability, nervousness, 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.

Intracranial pressure with papilloedema in children (pseudotumour cerebri) usually after treatment withdrawal, psychological dependence.

Ophthalmic: Corneal or scleral thinning, scleral perforation, exacerbation of ophthalmic viral or fungal disease, glaucoma, increased intra-ocular pressure, papilloedema, posterior subcapsular cataracts.

General: Hypersensitivity including anaphylaxis, leucocytosis, malaise, increase in blood coagulability, thromboembolism.

Withdrawal symptoms: Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. See "other special warnings and precautions". A "withdrawal syndrome" may also occur including arthralgia, conjunctivitis, fever, loss of weight, myalgia, painful itchy skin nodules and rhinitis.

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 the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard

4.9 Overdose

In the event of an overdosage no specific antidote is available. Treatment is supportive and symptomatic.
Serum electrolytes should be monitored

5.1 Pharmacodynamic properties

ATC CODE: H02A B06
Prednisolone is one of the highly potent glucocorticoid steroids having anti-inflammatory, hormonal and metabolic effects qualitatively similar to those of hydrocortisone. The effects of corticosteroids are numerous and widespread. They influence carbohydrate, protein and lipid metabolism, electrolyte and water imbalance, and the functions of the cardiovascular system, the kidney, skeletal muscle, the nervous system and other organs and tissues. Furthermore, the corticosteroids endow the organism with the capacity to resist many types of noxious stimuli and environmental change.

5.2 Pharmacokinetic properties

Absorption:

Prednisolone is readily absorbed from the gastrointestinal tract.

Distribution:
Peak plasma concentrations are obtained 1-2 hours after oral administration.
Prednisolone is extensively bound to plasma proteins, although less so than

hydrocortisone. Prednisolone crosses the placenta and small amounts are excreted in breast milk.

Metabolism: Prednisolone is mainly metabolised in the liver and has a usual plasma half-life of 2-3 hours. It has a biological half-life lasting several hours which makes it suitable for the alternate-day administration regimens which have been found to reduce the risk of adrenocortical insufficiency, yet provide adequate corticosteroid coverage in some disorders.
Its initial absorption, but not its overall bioavailability, is affected by food, hepatic or renal impairment and certain drugs.
Excretion: It is excreted in the urine as free and conjugated metabolites, together with an appreciable proportion of unchanged prednisolone.

5.3. Pre-clinical Safety Data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose

Maize Starch

Sodium Starch Glycollate

Stearic Acid

Magnesium Stearate

Colloidal silicon dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

5 years.

6.4. Special Precautions for Storage

Store below 25°C in a dry place, protect from light.

6.5. Nature and Contents of Container

PP tubes with LDPE caps containing 100, 250, 500, 1000 or 5000 tablets.

Al/PVC blisters containing 28 or 56 tablets.

Not all pack sizes may be marketed.

6.6. Instruction for Use, Handling and Disposal

No special instructions.

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire

WD18 9SS

Trading as: Co-pharma

8. MARKETING AUTHORISATION NUMBER(S)

PL 13606/0037

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28th January 1997

10 DATE OF REVISION OF THE TEXT

27/04/2017