SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prednisolone 5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of the active ingredient prednisolone.

Excipients with known effect

Each tablet contains 65 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White biconvex tablets. Engraved: 'APS' breakline '2402' on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Allergy and anaphylaxis: bronchial asthma, drug hypersensitivity reactions, serum sickness, angioneurotic oedema, anaphylaxis

Arteritis/ collagenosis: giant cell arteritis/ polymyalgia rheumatica, mixed connective tissue disease, polyarteritis nodosa, polymyositis

Blood disorders: haemolytic anaemia (auto-immune), leukaemia (acute and chronic lymphocytic), lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura.

Cardiovascular disorders: post-myocardial infarction syndrome, rheumatic fever with severe carditis

Endocrine disorders: primary and secondary adrenal insufficiency, congenital adrenal hyperplasia

Gastro-intestinal disorders: Crohn's disease, ulcerative colitis, persistent coeliac syndrome (coeliac disease unresponsive to gluten withdrawal), auto-immune chronic active hepatitis, multisystem disease affecting liver, biliary peritonitis

Hypercalcaemia: sarcoidosis, vitamin D excess

Infections (with appropriate chemotherapy): helminthic infestations, Herxheimer reaction, infectious mononucleosis, millary tuberculosis, mumps orchitis (adult), tuberculous meningitis, rickettsial disease.

Muscular disorders: polymyositis, dermatomyositis

Neurological disorders: infantile spasms, Shy-Drager syndrome, sub-acute demyelinating polyneuropathy

Ocular disease: scleritis, posterior uveitis, retinal vasculitis, pseudo-tumours of the orbit, giant cell arteritis, malignant ophthalmic Graves disease

Renal disorders: lupus nephritis, acute interstitial nephritis, minimal change glomerulonephritis

Respiratory disease: allergic pneumonitis, asthma, occupational asthma, pulmonary aspergillosis, pulmonary fibrosis, pulmonary alveolitis, aspiration of foreign body, aspiration of stomach contents, pulmonary sarcoid, drug induced lung disease, adult respiratory distress syndrome, spasmodic croup.

Rheumatic disorders: rheumatoid arthritis, polymyalgia rheumatica, juvenile chronic arthritis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease

Skin disorders: pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, pyoderma gangrenosum

Miscellaneous: sarcoidosis, hyperpyrexia, Behçets disease, immunosuppression in organ transplantation

4.2. Posology and method of administration

Posology

The following therapeutic guidelines should be kept in mind for all therapy with corticosteroids:

Corticosteroids are palliative symptomatic treatment by virtue of their anti-inflammatory effects; they are never curative.

The appropriate individual dose must be determined by trial and error and must be re-evaluated regularly according to activity of the disease.

As corticosteroid therapy becomes prolonged and as the dose is increased, the incidence of disabling side effects increases.

In general, initial dosage shall be maintained or adjusted until the anticipated response is observed.

The dose should be gradually reduced until the lowest dose which will maintain an adequate clinical response is reached.

Use of lowest effective dose may also minimise side-effects. Patients should be issued with a steroid treatment card and should be warned that treatment must not be stopped abruptly (see section 4.4).

In patients who have received more than physiological dose for 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 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 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 the 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 (month 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

(see section 4.4 and 4.8)

During prolonged therapy, dosage may need to be temporarily increased during periods of stress or during exacerbations of the disease (see section 4.4)

If there is lack of satisfactory clinical response to prednisolone tablets, the drug should be gradually discontinued and the patients transferred to alternative therapy.

Recommended doses and dose schedules

Intermittent dosage regimen A single dose of Prednisolone tablets in the morning on alternate days or at longer intervals is acceptable therapy for some patients. When this regimen is practical, the degree of pituitary-adrenal suppression can be minimised.

Specific dosage guidelines The following recommendations for some corticosteroid-responsive disorders are for guidance only. Acute or severe disease may require initial high dose therapy with reduction to the lowest effective maintenance dose as soon as possible. Dosage reductions should not exceed 5-7.5mg daily during chronic treatment.

Allergic and skin disorders: Initial doses of 5-15mg daily are commonly adequate.

Collagenosis: Initial doses of 20-30mg daily are frequently effective. Those with more severe symptoms may require higher doses.

Rheumatoid arthritis: The usual dose is 10-15 mg daily. The lowest daily maintenance dose compatible with tolerable symptomatic relief is recommended.

Blood disorders and lymphoma: An initial daily dose of 15-60mg is often necessary with reduction after an adequate clinical or haematological response. Higher doses may be necessary to induce remission in acute leukaemia.

Adults:
The initial dosage of Prednisolone Tablets may vary from 5 mg to 60 mg daily depending on the disorder being treated. Alternatively, it may be given as a single dose in the morning after breakfast or as a double dose on alternate days.

The usual maintenance range is 2.5 – 15 mg daily, but higher doses may be needed.

Alternate day therapy is the dosage regime of choice for long-term oral glucocorticoid therapy if disease controls allows. In this regimen a single dose is administered every other morning before 9.00 am to provide relief of symptoms whilst minimising adrenal suppression, protein catabolism and other adverse effects. Alternate day therapy is not appropriate for patients with established adrenal insufficiency.

Children:
Although appropriate fractions of the actual dose may be used, dosage will usually be determined by clinical response as in adults (see section 4.4).. Not normally recommended (owing to the adverse effect on growth), but the following may be used as a guide where treatment is considered essential. Where possible administration should take place on alternate days as a single dose.

Over 12 years: Three quarters of the adult dose.
Over 7 years: One half of the adult dose.
Over 1 year: One quarter of the adult dose.

Elderly:
The usual adult dosage is suitable, however it should be used with care as elderly patients are more susceptible to side-effects(see section 4.4).

Method of administration
For oral administration

4.3. Contraindications

- Prednisolone tablets are contraindicated in patients who have systemic infection unless specific anti-infective therapy is employed.
- Hypersensitivity to prednisolone or to any of the excipients listed in section 6.1.
- Prednisolone tablets are contraindicated in patients with ocular herpes simplex because of possible perforations.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4. Special warnings and precautions for use

A patient information leaflet should be supplied with this product.

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 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 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 and patients with systemic sclerosis because of possible risk of scleroderma renal crisis which can be fatal.

Tumorigenicity: direct tumour-inducing effects of the glucocorticoids are not known, but the particular risk that malignancies in patients undergoing immunosuppression with these or other drugs will spread more rapidly is a well-recognised problem (see section 4.5).

Calciphylaxis may occur very rarely during treatment with corticosteroids (see section 4.8). Although calciphylaxis is most commonly observed in patients who have end stage kidney failure, it has also been reported in patients taking corticosteroids who have minimal or no renal impairment and normal calcium, phosphate and parathyroid hormone levels. Patients/carers should be advised to seek medical advice if symptoms develop.

Caution is necessary when oral corticosteroids, including Prednisolone Tablets 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 the active tuberculosis can, however be prevented by the prophylactic use of anti-tuberculosis therapy.

- Inflammatory bowel disease: Symptoms recurred in a patient with Crohn's disease on changing from conventional to enteric-coated tablets of prednisolone. This was not an isolated occurrence in the author's unit, and it was advocated that only non-enteric coated prednisolone tablets should be used in Crohn's disease, and that the enteric coated form should be used with caution in any condition characterized by diarrhoea or a rapid transit time.

- Hypertension.

- Congestive heart failure.

- Liver failure.

- Hepatic disease: In patients with acute and active hepatitis, protein binding of the glucocorticoids will be reduced and peak concentrations of administered glucocorticoids increased. Elimination of prednisolone will also be impaired.There is an enhanced effect of corticosteroids in patients with cirrhosis.

- Renal insufficiency.

- Diabetes mellitus (or a family history of diabetes).
- Osteoporosis (post-menopausal females are particularly at risk).

- Corticosteroid requirements may be reduced in menopausal and post-menopausal women.

- Patients with a history of severe affective disorders and particularly those with a previous history of steroid-induced psychoses.

- Also existing emotional instability or psychotic tendencies may be aggravated by corticosteroids including Prednisolone.

- 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.

- Glaucoma (or a family history of glaucoma).

- Previous corticosteroid-induced myopathy.

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. Cushingoid side-effects are increasingly likely with doses above 7.5 mg daily. Frequent patient review is required to appropriately titrate the dose against disease activity (see section 4.2).

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.

In addition, 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. 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 mineralocorticoid 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.

Patients should carry "Steroid treatment" cards which give clear guidance on the precautions to be taken to minimize risk and which provide details of prescriber, drug, dosage and the duration of treatment. The drug must not be stopped abruptly (see section 4.2).

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 the 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 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. The effect of corticosteroids may be enhanced in patients with hypothyroidism and in those with chronic liver disease with impaired hepatic function.

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 responsiveness. Live vaccines should be postponed until at least 3 months after stopping corticosteroid therapy. (see section 4.5) The antibody response to other vaccines may be diminished.

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.

Systemic glucocorticoid treatment can cause severe exacerbation of bullous exudative retinal detachment and lasting visual loss in some patients with idiopathic central serous chorioretinopathy (see section 4.8).

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

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

Psychic derangements may appear when corticosteroids, including prednisolone, are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations (see section 4.8).

Raised intracranial pressure Raised intracranial pressure with papilloedema (pseudotumour cerebri) associated with corticosteroid treatment has been reported in both children and adults. The onset usually occurs after treatment withdrawal (see section 4.8).

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.

Paediatric population Corticosteroids cause dose related growth retardation in infancy, childhood and adolescence, which may be irreversible and therefore long-term administration of pharmacological doses should be avoided. If prolonged therapy is necessary, treatment should be limited to the minimum suppression of the hypothalamo-pituitary adrenal axis and growth retardation. The growth and development of infants and children should be closely monitored. Treatment should be administered where possible as a single dose on alternate days.

There is an increased risk of nuclear cataracts (see section 4.8).

Visual disturbance Visual disturbance 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.

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.

4.5. Interactions with other medicinal products and other forms of interaction

Hepatic microsomal enzyme inducers Drugs that include hepatic enzyme cytochrome P-450 (CYP) isoenzyme 3A4 such as rifampicin, rifabutin, carbamazepine, phenobarbital and other barbiturates, phenytoin, primidone and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced. Lack of expected response may be observed and dosage of prednisolone tablets may need to be increased.

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

Antacids The absorption of prednisolone may be reduced by large doses of some antacids such as magnesium trisilicate or aluminium hydroxide.

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

Other 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.

Anticoagulants Response to anticoagulants may be reduced or, less often, 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.

Antiepileptics carbamazepine, phenobarbital, phenytoin and primidone accelerate metabolism of corticosteroids and may reduce their effects.

Non-steroidal anti-inflammatory drugs Concomitant administration of ulcerogenic drugs such as indometacin during corticosteroid therapy may increase the risk of GI ulceration. Aspirin should be used cautiously in conjunction with glucocorticoids in patients with hypoprothrombinaemia. Although concomitant therapy with salicylate and corticosteroids does not appear to increase the incidence or severity of GI ulceration, the possibility of this effect should be considered.

Serum salicylate concentrations may decrease when corticosteroids are administered concomitantly. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and corticosteroids should be used concurrently with caution. Patients receiving both drugs should be observed closely for adverse effects of either drug.

Antibacterials Rifamycins accelerate metabolism of corticosteroids and thus may reduce their effect. Erythromycin inhibits metabolism of methylprednisolone and possibly other corticoids.
Prednisolone can lower plasma levels of isoniazid. Where a reduced response during concurrent use is noted, dosage adjustment of isoniazid may be necessary.

Antifungals Risk of hypokalaemia may be increased with amphotericin, therefore concomitant use with corticosteroids should be avoided unless corticosteroids are required to control reactions; ketoconazole inhibits metabolism of methylprednisolone and possibly other corticosteroids.

Antimuscarinics (Anticholinergics) Prednisolone has been shown to have antimuscarinic activity. If used in combination with another antimuscarinic drug, it could cause impairment to memory and attention in the elderly.

Antithyroids Prednisolone clearance is increased by the use of carbimazole and thiamazole.

Antivirals Ritonavir possibly increases plasma concentrations of prednisolone and other corticosteroids by reduction in clearance of prednisolone through the inhibition of P450 isoenzyme CYP3A4.

Cardiac Glycosides increased toxicity if hypokalaemia occurs with 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 adjustments should be considered when these drugs are administered concomitantly.

Cytotoxics Increased risk of haematological toxicity with methotrexate.

Liquorice Glycyrrhizin can delay the clearance of prednisolone.

Mifepristone Effect of corticosteroids may be reduced for 3-4 days after mifepristone.

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

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

Hormonal contraceptives Oral contraceptives increased prednisolone concentrations by 131%. May increase AUC and reduce clearance in oral contraceptives containing ethinylestradiol, mestranol, desogestrel, levonorgestrel, norgestrel or norethisterone.

Immunosuppressants Tumorigenicity: direct tumour-inducing effects of the glucocorticoids are not known, but the particular risk that malignancies in patients undergoing immunosuppression with these or other drugs will spread more rapidly is a well-recognised problem.

Somatropin Growth promoting effect may be inhibited

Sympathomimetics Increased risk of hypokalaemia of high doses of corticosteroids given with high doses of bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline

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 effects.

4.6. Fertility, 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 been observed in infants born to mothers treated with long-term prednisolone during pregnancy. 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. Patients with pre-eclampsia or fluid retention require close monitoring.

Breast-feeding:
Corticosteroids are excreted in small amounts in breast milk. Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risks to the infants.

However, doses of up to 40 mg 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

None known.

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 section 4.4)

The frequencies of adverse events are ranked according to the following:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data

System Organ Class	Frequency	Undesirable Effect
Infections and Infestations	Not known	Increases susceptibility to, and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see section 4.4), oesophageal candidiasis.

Blood and lymphatic system disorders	Not known	Leucocytosis.
Immune system disorders	Not known	Hypersensitivity including anaphylaxis has been reported.
Endocrine disorders	Not known	Suppression of the hypothalamic-pituitary-adrenal axis particularly in times of stress, as in trauma, surgery or illness, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea, Cushingoid facies, weight gain, impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy, manifestation of latent diabetes mellitus, Negative protein and calcium balance, increased appetite, Cushing's syndrome
Metabolism and nutrition disorders	Very rare	Calciphylaxis (see section 4.4)
	Not known	Sodium and fluid retention, hypokalaemic alkalosis, potassium loss, negative nitrogen and calcium balance, glucose intolerance and protein catabolism. Increase both high and low density lipoprotein cholesterol concentration in the blood, hyperglycaemia, dyslipidaemia.
Psychiatric disorders	Common	Irritability, depressed and labile mood, suicidal thoughts, psychotic reactions, mania, delusions, hallucinations, and aggravation of schizophrenia. behavioural disturbances, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia.
	Not known	Euphoria, depression, insomnia, psychological

		dependence.
Nervous system disorders	Not known	Dizziness, headache. Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy, epidural lipomatosis. vertebrobasilar stroke (exacerbation of giant cell arteritis, with clinical signs of evolving stroke has been attributed to prednisolone).
Eye disorders	Not known	Vision, blurred (see also section 4.4)
	Not known	Glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exophthalmos, exacerbation of ophthalmic viral or fungal diseases. Severe exacerbation of bullous exudative retinal detachment; lasting visual loss in some patients with idiopathic central serous chorioretinopathy (see section 4.4).
Ear and labyrinth disorders	Not known	Vertigo.
Cardiac disorders	Not known	Congestive heart failure in susceptible patients, increased risk of heart failure. Increased risk of cardiovascular disease, including myocardial infarction (with high dose therapy). Bradycardia (following high doses)
Vascular disorders	Not known	Thromboembolism, hypertension.
Gastrointestinal disorders	Not known	Dyspepsia, nausea, peptic ulceration with perforation and haemorrhage, abdominal distension, abdominal pain, diarrhoea, oesophageal ulceration, oesophageal candidiasis, acute pancreatitis
Skin and subcutaneous tissue disorders	Not known	Hirsutism, skin atrophy, bruising, striae,

		telangiectasia, acne, increased sweating, pruritis, rash, urticaria.
Musculoskeletal and connective tissue disorders	Not known	Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, tendinopathies (particularly of the Achilles and patellar tendons), myalgia, growth suppression in infancy, childhood and adolescence.
Renal and urinary disorders	Not known	Scleroderma renal crisis (see under Description of selected adverse reactions)
Reproductive system and breast disorders	Not known	Menstrual irregularity, amenorrhoea.
General disorders and administration site conditions	Not known	Impaired healing, fatigue and malaise.
Investigations	Not known	Increased intra-ocular pressure, may suppress reactions to skin tests.

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 and 4.2)

A steroid 'withdrawal syndrome' seemingly unrelated to adrenocortical insufficiency may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight and/or hypotension. These are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 7.5 mg prednisolone or equivalent) for greater than three 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 corticosteroids may be reduced rapidly to physiological doses. Once a daily dose equivalent to 7.5 mg 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 three weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 40 mg daily of prednisolone or equivalent for three 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 three weeks or less:

1. Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than three weeks.
2. When a short course has been prescribed within one year of cessation of long term therapy (months or years).
3. Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
4. Patients receiving doses of systemic corticosteroid greater than 40 mg daily of prednisolone (or equivalent).
5. Patients repeatedly taking doses in the evening.

Description of selected adverse reactions

Scleroderma renal crisis

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%)

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

4.9. Overdose

As most side effects of prednisolone are associated with prolonged treatment, acute overdosage is not an emergency and no specific treatment is recommended. Treatment is supportive and symptomatic. Serum electrolytes should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: CO5A A04 Products containing prednisolone.

Prednisolone has anti-inflammatory properties. It is thought to act by controlling the rate of synthesis of protein. It also influences carbohydrate and lipid metabolism as well as electrolyte and water balance. The cardiovascular system, kidneys, skeletal muscle and the nervous system are all affected by prednisolone.

5.2. Pharmacokinetic properties

Prednisolone is metabolised rapidly and apparently almost completely absorbed after oral administration; it reaches peak plasma concentrations after 1-3 hours. There is however wide inter-subject variation suggesting impaired absorption in some individuals.

Plasma half-life is about 3 hours in adults and somewhat less in children. Its initial absorption, but not its overall bioavailability, is affected by food. Prednisolone has a biological half-life lasting several hours, making it suitable for alternate-day administration regimens.

Prednisolone shows dose dependent pharmacokinetics, with an increase in dose leading to an increase in volume of distribution and plasma clearance. The degree of plasma protein binding determines the distribution and clearance of free, pharmacologically active drug. Reduced doses are necessary in patients with hypoalbuminaemia.

The following observations have been reported:

Oral availability	80 ± 11%
Urinary excretion	3 ± 2%
Plasma binding	75 ± 2%
Clearance	3.6 ± 0.8 ml/min kg
Volume of distribution	0.97 ± 0.11 1/kg
Half-life	36 ± 0.4 hours

Prednisolone is metabolised primarily in the liver to a biologically inactive compound. Liver disease prolongs the half-life of prednisolone and, if the patient has hypoalbuminaemia, also increases the proportion of unbound drug and may thereby increase adverse effects.

Prednisolone is excreted in the urine as free and conjugated metabolites, together with small amounts of unchanged prednisolone.

5.3. Preclinical safety data

Preclinical information has not been included because the safety profile of prednisolone has been established after many years of clinical use. Please refer to Section 4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Dextrin
Maize starch
Stearic acid (E570).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

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

6.5. Nature and contents of container

Polypropylene containers with polyethylene lids or amber glass bottles with plastic caps or HDPE containers with LDPE lids or child resistant caps in packs of 500, 1000 and 10 x 50.

PVC/PVdC hard tempered aluminium foil blister packs in packs of 28 and 30

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (and disposal)

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0276

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

14/11/2022

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