

Section 3 - Summary of Product Characteristics

Product Summary

1 Trade Name of the Medicinal Product

PREDNISOLONE TABLETS 5mg

2 Qualitative and Quantitative Composition

Each tablet contains 5mg Prednisolone PhEur.

3 Pharmaceutical Form

Red enteric/sugar-coated tablets.

Clinical Particulars

4.1 Therapeutic Indications

- 1) *Allergy and anaphylaxis*: Drug hypersensitivity reactions, serum sickness, angioneurotic oedema, anaphylaxis, bronchial asthma and occupational asthma.
- 2) *Arteritis/collagenosis*: Giant cell arteritis, mixed connective tissue disease, polyarteritis nodosa.
- 3) *Blood disorders*: Haemolytic anaemia (autoimmune), leukaemia (acute and lymphatic), malignant lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura, polymyositis.
- 4) *Cardiovascular disorders*: Post myocardial infarction syndrome, rheumatic fever with severe carditis.
- 5) *Endocrine disorders*: Primary and secondary adrenal insufficiency, congenital adrenal hyperplasia.
- 6) *Gastrointestinal disorders*: Crohn's disease, ulcerative colitis, persistent coeliac syndrome (coeliac disease unresponsive to gluten withdrawal), autoimmune chronic active hepatitis, multisystem disease affecting liver, biliary peritonitis.
- 7) *Hypercalcaemia*: Sarcoidosis, vitamin D excess.
- 8) *Infections (with appropriate chemotherapy)*: Helminthic infestations, Herxheimer reaction, infectious mononucleosis, biliary tuberculosis, mumps orchitis (adults), tuberculous meningitis, rickettsial disease.
- 9) *Muscular disorders*: Polymyositis, dermatomyositis.
- 10) *Neurological disorders*: Infantile spasms, Shy-Drager syndrome, sub-acute demyelinating polyneuropathy.
- 11) *Ocular disease*: Scleritis, posterior uveitis, retinal vasculitis, pseudo tumours of the orbit, giant cell arteritis, malignant ophthalmic Graves disease.
- 12) *Renal disorders*: Lupus nephritis, acute interstitial nephritis, minimal change nephrotic syndrome.
- 13) *Respiratory disease*: Allergic pneumonitis, bronchial 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.

14) *Rheumatic disorders*: Rheumatoid arthritis, polymyalgic rheumatica, juvenile chronic arthritis, systemic lupus erythematosus, dermatomyositis.

15) *Skin disorders*: Pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, pyoderma gangrenosum.

16) *Miscellaneous*: Hyperpyrexia, Behcets syndrome, immuno-suppression in organ transplantation, sarcoidosis.

4.2 Posology and Method of Administration

The initial dosage of prednisolone may vary from 5-60mg daily depending on the disorder being treated. Preferably taken as a single dose in the morning, after breakfast. Divided daily dosage may be employed if required.

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. Please see "other undesirable effects section".

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

Abrupt cessation of prolonged high dosage corticosteroid therapy is associated with a significant risk of potentially life-threatening adrenal insufficiency. (See section 4.4 Special Warnings and Precautions or use).

In general, initial dosage should be maintained or adjusted until the anticipated response is observed. The dose should then be gradually reduced until the lowest dose which will maintain an adequate clinical response is reached.

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

When the drug is to be stopped, it must be withdrawn gradually and not abruptly.

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

Intermittent dosage regimen: A single dose of prednisolone 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 initial dose is 10-15mg 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.

- Although appropriate fractions of the adult dose may be used, dosage will usually be determined by clinical response as in adults.

Children: Aged 1-6 years- One quarter the adult dose.

Aged 7-11 years- One half the adult dose.

Aged 12-17 years- Three quarters the adult dose.

Corticosteroids cause growth retardation in infancy, childhood and adolescence which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimise suppression of the hypothalamo-pituitary adrenal axis and growth retardation, treatment should be administered where possible as a single dose on alternate days.

- *Elderly:* Treatment of elderly patients, especially if long-term, should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age, particularly diabetes, hypertension, hypokalaemia, osteoporosis, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

For oral use.

4.3 Contraindications

Hypersensitivity to any ingredients in the formulation.

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

Systemic infections unless specific anti-infective therapy is employed.

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

Caution is necessary when corticosteroids, including prednisolone, are prescribed to patients with the following conditions and frequent patient monitoring is necessary:

- Diabetes mellitus or in those with a family history of diabetes.
- Glaucoma or in those with a family history of glaucoma.
- Hypertension or congestive heart failure.
- Liver failure.
- Osteoporosis: This is of special importance in post-menopausal females who are at particular risk.
- Patients with a history of severe affective disorders and particularly those with a previous history of corticosteroid induced psychoses.
- Peptic ulceration.
- Previous steroid myopathy.
- Renal insufficiency.
- Tuberculosis: Those with a history of, or X-ray changes characteristic of tuberculosis. The emergence of active tuberculosis can, however, be prevented by the prophylactic use of antituberculous therapy.
- Recent myocardial infarction (rupture).

- **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 special care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.
- **Measles:** Patients are advised to avoid exposure to measles, medical advice should be sought if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.
- **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.
- **The effect of corticosteroids may be enhanced in patients with hypothyroidism in those with chronic liver disease with impaired hepatic function.**
- **Live vaccines should not be given to individuals with impaired immune responsiveness.** The antibody response to other vaccines may be diminished.
- **Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping 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 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 Interactions with other Medicaments and other forms of Interaction

- 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.
- Rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, primidone, carbimazole and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced. Therefore it may be necessary to adjust the dose of prednisolone accordingly.
- The desired effects of hypoglycaemic agents (including insulin), antihypertensives and diuretics are antagonised by corticosteroids.
- The hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics, beta-2-agonists, theophylline 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.
- Ciclosporin increases the plasma concentration of prednisolone.
- 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 possibility of GI ulceration should be considered with concomitant use with any other NSAIDs.
- Antifungals: Increased risk of hypokalaemia with amphotericin. Avoid concomitant use. Ketoconazole reduces the metabolic and renal clearances of methylprednisolone, this may also occur with prednisolone.
- Mifepristone reduces the effect of corticosteroids for 3-4 days after administration.
- Methotrexate may have a steroid sparing effect. There is evidence that the toxicity of methotrexate is increased.
- 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.
- Oestrogens and progestogens increase plasma concentrations of corticosteroids.

4.6 Pregnancy and Lactation

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 and immunosuppression 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 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.

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. Monitoring of the infant for adrenal suppression is advised.

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.

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.

Fluid and electrolyte disturbance: Hypertension, nocturia, hypokalaemic alkalosis, potassium loss, sodium and water retention.

Musculoskeletal: Avascular osteonecrosis, osteoporosis, proximal myopathy, tendon rupture, vertebral and long bone fractures.

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

Neuropsychiatric: Aggravation of schizophrenia, depression, euphoria, insomnia, nervousness, intracranial pressure with papilloedema in children (pseudotumour cerebri) usually after treatment withdrawal, psychological dependence.

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

General: Hypersensitivity including anaphylaxis, leucocytosis, malaise, 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.

4.9 Overdose

Reports of acute toxicity are rare. There is no specific antidote and treatment is supportive and symptomatic. Serum electrolytes should be monitored.

Pharmacological Properties

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. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

5.2 Pharmacokinetic properties

Absorption: Prednisolone is readily and almost completely absorbed from the GI tract after oral administration.

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 Preclinical safety data

Not applicable.

Pharmaceutical Particulars

6.1 List of excipients

The tablet cores also contain lactose, maize starch, microcrystalline cellulose and magnesium stearate. The tablet coating contains acacia, beeswax, calcium carbonate, colloidal silicon dioxide, cyclosiloxane, gelatin, glycerides, hydroxypropylmethylcellulose, IMS, indigo carmine (E132), polydimethylsiloxane, polyethylene glycol, polyethylene glycol fatty acid ester, polyvinyl acetate

phthalate, ponceau 4R (E124), povidone, sodium alginate, sodium benzoate (E211), sodium hydrogen carbonate, sodium hydroxide, solvent ether, sorbic acid (E200), stearic acid, sucrose, sunset yellow (E110), talc, titanium dioxide (E171), triethyl citrate and water. The printing ink contains dimeticone, IMS, N-butyl alcohol, shellac, soya lecithin, titanium dioxide (E171) and water.

6.2 Incompatibilities

None known.

6.3 Shelf-life

Shelf-life

A three year shelf-life is claimed and our marketed products includes a three year expiry date.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage

Store in a cool dry place.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool. An alternative closure for polyethylene containers is a polypropylene, twist on, push down and twist off child-resistant, tamper-evident lid.

The product may also be supplied in blister packs in cartons:

- a) Carton: Printed carton manufactured from white folding box board.
- b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

The product may be contained in blister packs which enhances security of the pack increasing resistance to deliberate contamination, pilfering, etc.

Pack sizes: 28s, 30s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s, 250s, 500s, 1000s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for *temporary* storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6 Instructions for use/handling

Not applicable.

Administrative Data

7 MARKETING AUTHORISATION HOLDER

Name or style and permanent address of registered place of business of the holder of the Marketing Authorisation:

Actavis UK Limited
(Trading style: Actavis)
Whiddon Valley
BARNSTAPLE
N Devon EX32 8NS

8 Marketing Authorisation Number

PL 0142/0318

9 Date of First Authorisation/Renewal of Authorisation

11.4.91/3.9.02

10 DATE OF REVISION OF THE TEXT

February 2007