Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prednisolone 5 mg soluble tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg prednisolone as the sodium phosphate ester.

Excipients with known effect
Each tablet contains 37.6mg sodium and 4mg sodium benzoate (E 211).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soluble Tablet

Pink flat, round soluble tablets engraved with ƛ5 and break marked on the same side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prednisolone 5mg Soluble Tablets are indicated in adults and children.
A wide variety of diseases may sometimes require corticosteroid therapy. Some of the principal indications are:
- bronchial asthma, severe hypersensitivity reactions, anaphylaxis;
- rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease (excluding systemic sclerosis), polyarteritis nodosa;
- inflammatory skin disorders, including pemphigus vulgaris, bullous pemphigoid and pyoderma gangrenosum;
- minimal change nephrotic syndrome, acute interstitial nephritis;
- ulcerative colitis, Crohn's disease; sarcoidosis;
- rheumatic carditis;
- haemolytic anaemia (autoimmune), acute lymphoblastic and chronic lymphocytic leukaemia, malignant lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura;
- immunosuppression in transplantation.

4.2 Posology and method of administration

Posology
The lowest dosage that will produce an acceptable result should be used (see section 4.4); when it is possible to reduce the dosage, this must be accomplished by stages. 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.
Adults: The dose used will depend upon the disease, its severity and the clinical response obtained. The following regimens are for guidance only. Divided dosage is usually employed.

Short-term treatment: 20 to 30mg daily for the first few days, subsequently reducing the daily dosage by 2.5 or 5mg every two to five days, depending upon the response.

Rheumatoid arthritis: 7.5 to 10mg daily. For maintenance therapy the lowest effective dosage is used.

Most other conditions: 10 to 100mg daily for one to three weeks, then reducing to the minimum effective dosage.

Paediatric population: Fractions of the adult dosage may be used (e.g. 75% at 12 years, 50% at 7 years and 25% at 1 year) but clinical factors must be given due weight.

Prednisolone Soluble Tablets may be given early in the treatment of acute asthma attacks in children. For children over 5 years use a dose of 30-40mg prednisolone. For children aged 2-5 years use a dose of 20mg prednisolone. Those already receiving maintenance steroid tablets should receive 2mg/kg prednisolone up to a maximum dose of 60mg. The dose of prednisolone may be repeated for children who vomit; but intravenous steroids should be considered in children who are unable to retain orally ingested medication. Treatment for up to three days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery. There is no need to taper the dose at the end of a short course of treatment. If treatment is given for a longer period, withdrawal should not be abrupt (see Section 4.4).
For children under 2 years, Prednisolone Soluble Tablets can be used early in the management of moderate to severe episodes of acute asthma in the hospital setting, at a dose of 10mg for up to three days.

Method of Administration: For oral use only
Prednisolone Soluble Tablets are best taken dissolved in water, but they can be swallowed whole without difficulty. When dissolved in water the resulting solution must be drunk immediately by the patient.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Systemic infections, unless specific anti-infective therapy is employed.
- Live virus immunisation.
- Ocular herpes simplex because of possible perforation.

4.4 Special warnings and precautions for use

In patients who have received more than physiological doses of systemic corticosteroids (approximately 7.5mg 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 corticosteroid may be reduced rapidly to physiological doses. Once a daily dose equivalent to 7.5mg 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 40mg 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:
• Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than three 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 or in whom corticosteroids have been stopped following prolonged therapy, may need corticosteroids to be temporarily reintroduced.
• Patients receiving doses of systemic corticosteroid greater than 40mg daily of prednisolone (or equivalent).
• Patients repeatedly taking doses in the evening.

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

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Suppression of the HPA axis and other 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).

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.

Anti-inflammatory/immunosuppressive effect and infection
Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Chronic immunosuppression (e.g. in the setting of organ transplantation) has been associated with an increased risk of malignancy.

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The resultant opportunistic infections may be fatal. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients 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. If the patient is a child, parents must be given the above advice. 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 three months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment.

Corticosteroids should not be stopped and the dose may need to be increased.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Live vaccines should not be given to individuals with impaired immune responsiveness caused by high doses of corticosteroids. The antibody response to other vaccines may be diminished.

Because of the possibility of fluid retention, care must be taken when corticosteroids are administered to patients with renal insufficiency or hypertension or congestive heart failure.

Corticosteroids may worsen diabetes mellitus, osteoporosis, hypertension, glaucoma and epilepsy and therefore patients with these conditions or a family history of them should be monitored frequently.

Care is required and frequent patient monitoring necessary where there is a history of severe affective disorders (especially a previous history of steroid psychosis), previous steroid myopathy, peptic ulceration, hypothyroidism, recent myocardial infarction or patients with a history of tuberculosis.

In patients with liver failure, blood levels of corticosteroid may be increased, as with other drugs which are metabolised in the liver. Frequent patient monitoring is therefore necessary.

Use in the Elderly: The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most adverse reactions resolve after either dose reduction or withdrawal of the medicine, 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 a 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.

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.

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

Excipients
This medicinal product contains 37.6 mg sodium per dose, equivalent to 1.88% of the WHO recommended maximum daily intake for sodium. The maximum daily dose of this product is equivalent to 37.6% of the WHO recommended maximum daily intake for sodium. Prednisolone Soluble Tablets is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

This medicine contains 4 mg of sodium benzoate (E 211) in each tablet which can cause an increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

4.5 Interaction with other medicinal products and other forms of interaction

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, ephedrine and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Mifepristone may reduce the effect of corticosteroids for 3-4 days.

Erythromycin and ketoconazole may inhibit the metabolism of some corticosteroids.

Ciclosporin increases plasma concentration of prednisolone. The same effect is possible with ritonavir.

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

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

The growth promoting effect of somatotropin may be inhibited by the concomitant use of corticosteroids.

Steroids may reduce the effects of anticholinesterases in myasthenia gravis and cholecystographic x-ray media.

The efficacy of coumarin anticoagulants and warfarin may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Concomitant use of aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with corticosteroids increases the risk of gastro-intestinal bleeding and ulceration.

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

The hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced by corticosteroids. The risk of hypokalaemia is increased with theophylline and amphotericin. Corticosteroids should not be given concomitantly with amphotericin, unless required to control reactions.

The risk of hypokalaemia also increases if high doses of corticosteroids are given with high doses of bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline. The toxicity of cardiac glycosides is increased if hypokalaemia occurs with corticosteroids.

Concomitant use with methotrexate may increase the risk of haematological toxicity.

High doses of corticosteroids impair the immune response and so live vaccines should be avoided (see also section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy
The ability of corticosteroids to cross 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 intrauterine growth retardation.

Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

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

Depression of hormone levels has been described in pregnancy but the significance of this finding is not clear.

Breast-feeding
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.

Fertility
No data available

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamo-pituitary-adrenal (HPA) suppression, correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see section 4.4).

Adverse reactions are listed as per System Organ Class. The following side effects may be associated with the long-term systemic use of corticosteroids with the following frequency:
Not known (cannot be estimated from available data)

System organ class	Undesirable effects
Infections and infestations	Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see section 4.4).
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.
Blood and lymphatic system disorders	Leukocytosis
Immune system disorders	Hypersensitivity including anaphylaxis has been reported.
Endocrine disorders	Suppression of the HPA axis. Cushingoid. Impaired carbohydrate intolerance with increased requirement for anti-diabetic therapy, manifestation of latent diabetes mellitus.
Metabolism and nutrition disorders	Sodium and water retention, hypokalaemia, alkalosis hypokalaemic , increased appetite, negative protein and calcium balance.
Psychiatric disorders[a]	Euphoric mood, drug dependence, depressed mood, insomnia, schizophrenia.
Nervous system disorders	Dizziness, headache. Epilepsy.
Eye disorders	Glaucoma, papilloedema, cataract subcapsular , central serous chorioretinopathy, exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases and vision blurred (see also section 4.4).
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Myocardial rupture following recent myocardial infarction. Congestive cardiac failure (in susceptible patients). Bradycardia*
Vascular disorders	Hypertension, embolism.
Respiratory, thoracic and mediastinal disorders	Hiccups
Gastrointestinal disorders	Dyspepsia, nausea, vomiting, abdominal distension, abdominal pain, diarrhoea, oesophageal ulceration, candidiasis, pancreatitis acute. Peptic ulcer with perforation and haemorrhage.
Skin and subcutaneous tissue disorders	Skin Atrophy, skin striae, acne, telangiectasia, hyperhidrosis, rash, pruritus, urticaria, hirsutism.
Musculoskeletal and connective tissue disorders	Myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, myalgia.
Renal and urinary disorders	Scleroderma renal crisis*
Reproductive system and breast disorders	Menstruation irregular, amenorrhoea.
General disorders and administration site conditions	Impaired healing, malaise.
Investigations	Weight increased.
Injury, poisoning and procedural complications	Tendon rupture, contusion (bruising).

*Following high doses

a) 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), behavioural disturbances, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia

have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.
*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%)

Withdrawal Symptoms
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4).

A 'withdrawal syndrome' may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

In some instances, withdrawal symptoms may involve or resemble a clinical relapse of the disease for which the patient has been undergoing treatment.

Other effects that may occur during withdrawal or change of corticosteroid therapy include benign intracranial hypertension with headache and vomiting and papilloedema caused by cerebral oedema.

Latent rhinitis or eczema may be unmasked.

Paediatric population:
Increased intracranial pressure with papilloedema in children (pseudotumour cerebri) -usually after treatment withdrawal.

Growth retardation in infancy, childhood and adolescence.

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 HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Treatment is unlikely to be needed in cases of acute overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB06

Prednisolone Soluble Tablets contain the equivalent of 5mg of prednisolone in the form of the 21-disodium phosphate ester. Prednisolone sodium phosphate is a synthetic glucocorticoid with the same general properties as prednisolone itself and other compounds classified as corticosteroids. Prednisolone is four times as active as hydrocortisone on a weight for weight basis.

Prednisolone sodium phosphate is very soluble in water, and is therefore less likely to cause local gastric irritation than prednisolone alcohol, which is only slightly soluble. This is important when high dosages are required, as in immunosuppressive therapy.

5.2 Pharmacokinetic properties

Absorption
Prednisolone is readily absorbed from the gastrointestinal tract with peak plasma concentrations achieved by 1-2 hours after an oral dose. Plasma prednisolone is mainly protein bound (70-90%), with binding to albumin and corticosteroid-binding globulin. The plasma half-life of prednisolone, after a single dose, is between 2.5-3.5 hours.

Distribution
The volume of distribution and clearance of total and unbound prednisolone are concentration dependent and this has been attributed to saturable protein binding over the therapeutic plasma concentration range.

Biotransformation

Prednisolone is extensively metabolised, mainly in the liver, but the metabolic pathways are not clearly defined.

Elimination
Over 90% of the prednisolone dose is excreted in the urine, with 7-30% as free prednisolone and the remainder being recovered as a variety of metabolites.

5.3 Preclinical safety data

No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Acid Citrate
Sodium Hydrogen Carbonate
Saccharin Sodium
Povidone
Sodium Benzoate
Erythrosine (E127)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The tablets are foil strip packed and supplied in cartons of 30 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1142/034/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 21st December 2018

10 DATE OF REVISION OF THE TEXT

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