Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg hydrocortisone

Excipients with known effect:
Each tablet contains 146.75 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White to off white, elliptical shape, flat, bevelled edge tablet with “BL 10” on one side and crossed break lines on other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Corticosteroid

- For use as replacement therapy in congenital adrenal hyperplasia in children.
- Pre-operatively, and during serious trauma or illness in children with known adrenal insufficiency or doubtful adrenocortical reserve.

4.2 Posology and method of administration

Posology

Dosage must be individualised according to the response of the individual patient

Replacement therapy
Children: In chronic adrenocortical insufficiency, the dosage should be approximately 0.4 to 0.8mg/kg/day in two or three divided doses, adjusted to the needs of the individual child.

In patients requiring replacement therapy, the daily dose should be given when practicable, in two doses. The first dose in the morning should be larger than the second dose in the evening, thus simulating the normal diurnal rhythm of cortisol secretion.

Use in serious trauma or illness with known adrenal insufficiency or doubtful adrenocortical reserve
Children: Doses are generally higher than that used for chronic adrenocortical insufficiency and should be selected as appropriate for the clinical situation. Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g. surgery, infection, trauma). During stress it may be necessary to increase the dosage temporarily

Pre-operative use:
Anaesthetists must be informed if the patient is taking corticosteroids or has previously taken corticosteroids.

When long term treatment is to be discontinued, the dose should be gradually reduced over a period of weeks or months, depending on dosage and duration of therapy (see section 4.4, Special Warnings and Precautions for Use).

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 titrate the dose against disease activity

Method of administration
For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Contraindicated in infections including systemic infections where specific anti-infective therapy has not been started.

High doses of corticosteroids impair the immune response to vaccines. Therefore the concomitant administration of live vaccines with corticosteroids should be avoided.

4.4 Special warnings and precautions for use

Adrenal suppression

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

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.

Anti-inflammatory / immunosuppressive effects and infection

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

Corticosteroids may activate latent amoebiasis or strongyloidiasis or exacerbate active disease. Therefore it is recommended that latent or active amoebiasis and strongyloidiasis be ruled out before initiating corticosteroid therapy in any patient at risk of or with symptoms suggestive of either condition.

Caution should be exercised in immunocompromised patients.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children receiving hydrocortisone tablets) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster. 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.

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.

Live vaccines should not be given to individuals with impaired immune responsiveness caused by high doses of corticosteroids. Killed vaccines or toxoids may be given though their effects may be attenuated.

Corticosteroids should be used with caution in: non-specific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer. Particular care is required when prescribing systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary:

a) Osteoporosis (postmenopausal females are particularly at risk);

b) hypertension or congestive heart failure;

c) existing or previous history of severe affective disorders (especially previous history of steroid psychosis);

d) diabetes mellitus (or a family history of diabetes);

e) previous history of tuberculosis or characteristic appearance on a chest x-ray. The emergence of active tuberculosis can, however, be prevented by the prophylactic use of anti-tuberculous therapy;

f) glaucoma (or family history or glaucoma);

g) previous corticosteroid-induced myopathy;

h) liver failure;

i) renal insufficiency;

j) epilepsy;

k) peptic ulceration;

l) recent myocardial infarction

During treatment, the patient should be observed for psychotic reactions, weakness, electrocardiographic changes, hypertension and untoward hormonal effects.

Corticosteroids should be used with caution in patients with hypothyroidism.

Children: Corticosteroids cause growth retardation in infancy, childhood and adolescence, this may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time, retardation (see section 4.2, Posology and method of administration)

Withdrawal symptoms:
In patients who have received more than physiological doses of systemic corticosteroids (approximately 40 mg hydrocortisone) 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 hypothalamic- pituitary adrenal (HPA) suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 30 mg hydrocortisone 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 160 mg hydrocortisone 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
- patients receiving doses of systemic corticosteroid greater than 160 mg hydrocortisone
- patients repeatedly taking doses in the evening.

Patients/and or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see Section 4.8 Undesirable effects). 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 Interaction with other medicinal products and other forms of interaction), 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of corticosteroids may be enhanced and the therapeutic effects reduced by ephedrine, certain barbiturates (e.g. phenobarbital) and by phenytoin, rifampicin, rifabutin, primidone, carbamazepine and aminoglutethimide.

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

Erythromycin and ketoconazole may inhibit the metabolism of corticosteroids.

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.

Ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal (see 4.4 'Special warnings and precautions for use').

Ritonavir may increase the plasma concentration of hydrocortisone.

Oestrogens and other oral contraceptives increase the plasma concentration of corticosteroids, and dosage adjustments may be required if oral contraceptives are added to or withdrawn from a stable dosage regimen.

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

The desired actions of hypoglycaemic drugs (including insulin), antihypertensives and diuretics are antagonised by corticosteroids.
The effectiveness of coumarin anticoagulants may be affected by concurrent corticosteroid therapy and close

monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Serum levels of salicylates, such as aspirin and benorilate, may increase considerably if corticosteroid therapy is withdrawn, possibly causing intoxication. Concomitant use of salicylates or of non-steroidal anti-inflammatory drugs (NSAIDs) with corticosteroids increases the risk of gastrointestinal bleeding and ulceration.

The potassium-depleting effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced by corticosteroids and signs of hypokalaemia should be looked for during their concurrent use. 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 sympathomimetics e.g. bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline. The toxicity of cardiac glycosides, e.g. digoxin, is increased if hypokalaemia occurs.

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, Special Warnings and Precautions for Use)

4.6 Fertility, pregnancy and lactation

Pregnancy
The ability of corticosteroids to cross the placenta varies between individual drugs; however, cortisone readily crosses the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids 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.

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 states

Breast-feeding
Corticosteroids are excreted in breast milk, although no data are available for hydrocortisone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression. Mothers taking pharmacological doses of corticosteroids should be advised not to breast-feed. Any maternal treatment should be carefully documented in the infant's medical records to assist in follow up.

Fertility
Patients with adrenal insufficiency have been shown to have reduced parity, which is most likely due to the underlying disease, but there is no indication that hydrocortisone in doses for replacement therapy will affect fertility.

4.7 Effects on ability to drive and use machines

Hydrocortisone has minor influence on the ability to drive and use machines. Fatigue and episodes of short lasting vertigo have been reported.

Untreated and poorly replaced adrenal insufficiency may affect the ability to drive and use machines.

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamicpituitary- adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see section 4.4, Special Warnings and Precautions for Use).

The following side effects may be associated with the long-term systemic use of corticosteroids.

Anti-inflammatory and immunosuppressive effects:
Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, and recurrence of dormant tuberculosis treatment (see section 4.4, Special Warnings and Precautions for Use).

Gastrointestinal:
Dyspepsia, peptic ulceration with perforation and haemorrhage, abnormal distension, oesophageal ulceration, candidiasis, acute pancreatitis.

Musculoskeletal:
Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture.

Fluid and electrolyte disturbance:
Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis.

Dermatological:
Impaired healing, skin atrophy, bruising, striae, acne, telangiectasia.

Endocrine / metabolic:
Suppression of the hypothalamo-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea.
Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, negative protein and calcium balance, and increased appetite.

Neuropsychiatric:
Euphoria, psychological dependence, depression, insomnia and aggravation of schizophrenia. Increased intracranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy.

Ophthalmic:
Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.

Cardiovascular:
Myocardial rupture following recent myocardial infarction.

General:
Hypersensitivity, including anaphylaxis has been reported. Nausea, malaise, leucocytosis, thromboembolism.

Withdrawal symptoms:
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute renal insufficiency, hypotension and death (see section 4.4 Special warnings and precautions for use). A withdrawal syndrome may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin modules and weight loss.

Psychiatric disorders:
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.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overdosage may cause nausea and vomiting, sodium and water retention, hyperglycaemia and occasional gastrointestinal bleeding. Treatment need only be symptomatic although cimetidine (200-400 mg by slow intravenous injection every 6 hours) or ranitidine (50 mg by slow intravenous injection every 6 hours) may be administered to prevent gastrointestinal bleeding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: H02AB02 Systemic Hormonal Preparations (excluding sex hormones and insulins); Corticosteroids for Systemic Use; Plain; Hydrocortisone.

Hydrocortisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally-occurring and synthetic, which are readily absorbed from the gastro- intestinal tract.

Hydrocortisone is believed to be the principal corticosteroid secreted by the adrenal cortex. Naturally-occurring glucocorticosteroids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. They are also used for their potent anti- inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition they modify the body's immune responses to diverse stimuli.

5.2 Pharmacokinetic properties

Hydrocortisone is readily absorbed from the gastro-intestinal tract and 90% or more of the drug is reversibly bound to protein.
The binding is accounted for by two protein fractions. One, corticosteroid-binding globulin is a glycoprotein; the other is albumin.

Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol which are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.

Half-life of hydrocortisone is about 1.5 hours.

5.3 Preclinical safety data

Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous
Lactose monohydrate
Cellulose, microcrystalline
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/PVDC//aluminium blister packs containing 30 tablets.

Amber coloured glass bottles with white enamelled tin closures containing 50 or 100 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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