Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone Hualan 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg hydrocortisone.

Excipient with known effect:

Each tablet contains 95.80 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White oval shaped tablets of about 9.8 – 10.2 mm in length and 4.2 - 4.6 mm in width, engraved 'H5' on one side and a score in the middle of the other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use as replacement therapy in primary or secondary adrenocortical insufficiency and prevention of an acute adrenocortical crisis.

Pre-operatively, and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenocortical reserve.

4.2 Posology and method of administration

Posology
Dosage must be individualized according to the response of the individual patient. The lowest possible dosage should be used.

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.

If the drug is to be stopped after more than a few days of treatment, it should be withdrawn gradually.

Chronic adrenocortical insufficiency
A dosage of 20-30 mg a day is usually recommended, sometimes together with 4-6 g of sodium chloride or 50-300 micrograms of fludrocortisone daily. When immediate support is mandatory, one of the soluble adrenocortical corticosteroid preparations (e.g. dexamethasone sodium phosphate), which may be effective within minutes after parenteral administration, can be life-saving.

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

Appropriate strength of formulation should be chosen based on the prescribed dose and appropriate formulation should be chosen based on the child's capability to swallow and availability of formulations.

Elderly: treatment of elderly patients, particularly if long term, should be planned to bear in mind the more serious consequences of the common side effects of corticosteroids in old age, especially osteoporosis, diabetes, hypertension, susceptibility to infection and thinning of the skin.

Method of administration
For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute infectious processes: viral infections and systemic fungal infections (bacterial infections, see section 4.4).
- Tropical worm infections.
- After vaccination with live attenuated virus (see section 4.4).

4.4 Special warnings and precautions for use

Adrenal suppression and withdrawal
Corticosteroid therapy should be used only when simpler proven diagnosis and therapy is not feasible or has failed (unless there is a life-threatening situation). The lowest possible dosage of corticosteroids should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Drug-induced secondary adrenocortical insufficiency may result from too rapid a withdrawal of corticosteroids and may be minimised 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, corticosteroid therapy should be reinstated. If the patient is receiving steroids already, the dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

Anti-inflammatory/immunosuppressive effects and infections
Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions due to amphotericin. Moreover, there have been cases reported in which concomitant use of amphotericin and hydrocortisone was followed by cardiac enlargement and congestive failure.

Administration of live virus vaccines is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunisation procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, i.e., for Addison's disease.

The use of hydrocortisone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive prophylactic chemotherapy.

In cerebral malaria, the use of corticosteroids is associated with prolongation of coma and higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise infection in patients on corticosteroids.

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.

Steroid therapy might impair prognosis in surgery by increasing the hazard of infection. If infection is suspected, appropriate antibiotic therapy must be administered, usually in larger than ordinary doses.

Caution should be exercised in immunocompromised patients.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. The risk of developing a disseminated infection varies among individuals and may be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. Exposed patients should be advised to seek medical advice without delay. If exposed to measles, prophylaxis with pooled immunoglobulin (IG) may be indicated. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. (See the respective package inserts for IG and VZIG for complete prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.

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.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal ulceration and perforation.

Regular ophthalmic monitoring is recommended.

Cardiovascular system
Literature reports suggest an apparent association between use of corticosteroids and left ventricular free-wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Fat embolism has been reported as a possible complication of hypercortisonism.

Gastrointestinal system
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; renal insufficiency; hypertension, diabetes or in those with a family history of diabetes, congestive heart failure, previous steroid myopathy, glaucoma (or family history of glaucoma), osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastro-intestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent.
There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Paediatric population
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.
Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored.

Hypertrophic cardiomyopathy was reported after administration of hydrocortisone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

Psychiatric warnings
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.

Fertility
Corticosteroids may increase or decrease motility and number of spermatozoa in some patients.

Excipients
Hydrocortisone Hualan tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Phenytoin, ephedrine, rifabutin, carbamazepine, aminoglutethimide, barbiturates, and rifampicin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiological activity, thus requiring adjustment in corticosteroid dosage.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids in inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

Ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalaemia. Moreover, corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false negative results.

Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypopropthrombinaemia.

Hydrocortisone, in combination with diuretics increases the risk of hypokalaemia.

Glucocorticoids may increase the necessary quantity of insulin or oral antidiabetics.

Additive ulcerogenic effects should be considered when taking hydrocortisone with ulcerogenic agents (e.g. NSAIDs).

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
Since human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, or women of child-bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or foetus. Hydrocortisone crosses the placenta. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadreanalism.

Breast-feeding
Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacological doses of corticosteroids should be advised not to breast-feed.

4.7 Effects on ability to drive and use machines

Hydrocortisone Hualan tablets can have an influence on the ability to drive and use machines. When driving vehicles or operating machinery, it should be taken into account the possibility of the occurrence of muscle weakness, muscle atrophy, and mood changes (euphoria, depression).

4.8 Undesirable effects

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 (frequency cannot be estimated from the available data).

There are not many side effects or complications, but undesirable effects are inherent to the corticosteroid therapy. With a good dose of hydrocortisone replacement therapy, the risk of the following side effects is low.

Infections and infestations
Not known: Reduced resistance, which increases the risk of infections (opportunistic), an unfavourable course of infections (sepsis and reactivation of latent tuberculosis and parasitic infections such as amoebiasis and strongyloidiasis), masking of warning symptoms of sepsis and perforation.

Blood and lymphatic system disorders
Not known: Erythrocytosis and granulocytosis, lymphoma and eosinopenia.

Immune system disorders
Not known: Hypersensitivity or anaphylactic reactions.

Endocrine disorders
Not known: Inhibition of hypothalamic-pituitary-adrenal axis function (due to negative feedback by exogenous steroid) with risk of adrenal insufficiency when the patient is exposed to stress (trauma, surgery, infection), development of Cushing's syndrome.

Metabolism and nutrition disorders
Not known: Sodium and fluid retention, potassium decrease with hypokalaemic alkalosis, centripetal obesity (face, trunk) enhanced by increased appetite.

Psychiatric disorders
Not known: Euphoric mood, anxiety, depression, psychosis.

Nervous system disorders
Not known: Increased intracranial pressure with papilledema (pseudotumor cerebri), particularly in children during or shortly after rapid withdrawal, insomnia.

Eye disorders
Not known: Posterior subcapsular cataract, glaucoma, vision blurred (see section 4.4).

Cardiac disorders
Not known: Congestive heart failure in predisposed patients, hypertrophic cardiomyopathy in prematurely born infants.

Vascular disorders
Not known: Hypertension.

Gastrointestinal disorders
Not known: Oesophagitis, peptic ulcer with increased risk of bleeding and (masked) perforation, pancreatitis.

Skin and subcutaneous tissue disorders
Not known: Skin atrophy with large bruising ("easy bruising"), erythema of the face, acne and hirsutism, impaired wound healing, suppressed skin reactions to skin tests, allergic reactions such as urticaria.

Musculoskeletal and connective tissue disorders
Not known: Muscle weakness and muscle atrophy (steroid myopathy), risk of osteoporosis with compression fractures of vertebrae, aseptic bone necrosis, especially of the femoral head, growth retardation in children.

Reproductive system and breast disorders
Not known: Menstrual cycle abnormal.

Investigations
Not known: Decreased glucose tolerance, resulting in latent diabetes, increased need for oral hypoglycaemic agents or insulin in diabetics, negative nitrogen balance due to protein degradation, weight increased.

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

Anaphylactic and hypersensitivity reactions may be treated with adrenaline, positive-pressure artificial respiration and aminophylline. The patient should be kept warm and quiet.
Treatment is probably not indicated for reactions due to chronic poisoning unless the patient has a condition that would render him unusually susceptible to ill effects from corticosteroids. In this case, symptomatic treatment should be instituted as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic Hormonal Preparations (excluding sex hormones and insulins); Corticosteroids for Systemic Use; Plain; Hydrocortisone. ATC Code: H02AB09

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

Absorption and distribution
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.

Biotransformation
Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol.

Elimination
The mean plasma half-life of hydrocortisone is about 1.5 hours.
The metabolites are mainly excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Maize starch

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/aluminium blister containing 28, 30, 50, 56, 60, 84, 90, 100, 112 tablets per carton.
Not all pack sizes may be marketed.

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

Hualan Pharmaceuticals Limited
16/17 College Green
Dublin 2
Dublin

D02 V078
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23341/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th June 2024

10 DATE OF REVISION OF THE TEXT