# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone Hualan 15 mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg hydrocortisone.

Excipient with known effect:

Each tablet contains 136.20 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.

White, oval shaped tablets of about 11.3 – 11.7 mm in length and 4.8 – 5.2 mm in width, engraved 'HC15' 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

Replacement therapy of adrenocortical insufficiency in adults, children and adolescents (from birth to < 18 years of age).

### 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.

The daily dose should be split into two to three doses. The first dose in the morning should be higher than the last dose, to simulate the normal diurnal rhythm of cortisol secretion. In the case of 2 doses this is in general distributed over 2/3 in the morning and 1/3 in the evening. In the case of 3 doses the morning dose is in general twice as high as the midday and evening dose.

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If the drug is to be stopped after more than a few days of treatment, it should be withdrawn gradually (see section 4.4).

Missed dose
If a dose of Hydrocortisone Hualan tablets is missed, that dose should be administered as soon as possible, as well as their next dose at the usual time, even if this means that two doses are administered at the same time.

*Replacement therapy in adrenal insufficiency in adults*
The usual dose varies between 15 mg and 30 mg of hydrocortisone per day divided in 2-3 doses.

Daily doses in excess of 20 mg have been linked to increased long term mortality and should be avoided if possible, unless clinically indicated or else assessed with a hydrocortisone day curve as per local policies.

*Replacement therapy in adrenal insufficiency in children and adolescents < 18 years of age*
Recommended daily doses are 8-10 mg/$m^2$/day, typically in three divided doses. Generally, the first dose is twice as high as the second and third dose, 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. For patients unable to swallow tablets, other pharmaceutical forms are available and may be more appropriate.

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

Pre-operatively, anaesthetists must be informed if the patient is taking corticosteroids or has previously taken corticosteroids.

In less severe situations when parenteral administration of hydrocortisone is not required, for instance low grade infections, moderate fever of any aetiology and stressful situations such as minor surgical procedures, there should be high awareness of the risk of developing acute adrenal insufficiency, and the normal oral daily replacement dose should be increased temporarily; the hydrocortisone total daily dose should be increased by doubling or tripling the usual dose. Once the intercurrent illness episode is over, patients can return to the normal replacement dose of hydrocortisone.

In severe situations, an increase in dose is immediately required and oral administration of hydrocortisone must be replaced with parenteral treatment. Parenteral administration of hydrocortisone is warranted during transient illness episodes such as severe infections, in particular gastroenteritis associated with vomiting and/or diarrhoea, high fever of any aetiology or extensive physical stress, such as for instance serious accidents and surgery under general anaesthesia. Where parenteral hydrocortisone is required, the patient should be treated in a facility with resuscitation facilities in case of evolving adrenal crisis.

*Renal impairment*
There is no need for dosage adjustment in patients with mild to moderate renal impairment. In patients with severe renal impairment monitoring of the clinical response is recommended and dose adjustment may be required.

*Hepatic impairment*
There is no need for dose adjustment in mild to moderate hepatic impairment. In case of severe hepatic impairment, the functional liver mass decreases and thus the metabolising capacity for hydrocortisone. Therefore, monitoring of the clinical response is recommended, and dose adjustment may be required.

*Elderly*
In case of low body weight due to age, it is recommended to monitor the clinical response, and a lower dose may be necessary. The dose should be reviewed regularly to avoid over-replacement and associated side effects since there is a reducing requirement with age.
Method of administration

For oral use.

The tablets, or fractions, should be taken orally with a glass of water upon awakening, preferably in an upright position, and on an empty stomach. The tablets should not be chewed or crushed. If more than one administration per day is required, the morning dose should be taken as directed; additional doses may be taken with or without food.

**4.3 Contraindications**

Hypersensitivityto the active substance or to any of the excipients listed in section 6.1.

**4.4 Special warnings and precautions for use**

During therapy with hydrocortisone it is necessary to carefully adjust the treatment to the individual patient, including checks of weight, blood pressure and electrolytes. The lowest possible dosage of corticosteroids should be used and when reduction of the dosage is possible, the reduction should be gradual (see section 4.2).

Patients are advised to carry with them a card listing the details of their treatment with corticosteroids. It is also advisable to discuss the treatment, its effects, and the precautions to be taken with those close to them.

Treatment of adrenocortical insufficiency often warrants additional treatment with mineralocorticosteroids.

*Acute adrenal insufficiency (Addison crisis)*
Acute adrenal insufficiency may develop in patients with known adrenal insufficiency who are on inadequate daily doses or in situations with increased cortisol need. Adrenal crisis can develop in patients with acute adrenal insufficiency. Therefore, patients should be advised of the signs and symptoms of acute adrenal insufficiency and of adrenal crisis and the need to seek immediate medical attention. Sudden discontinuation of therapy with hydrocortisone risks triggering an adrenal crisis and death. During adrenal crisis parenteral, preferably intravenous administration of hydrocortisone in high doses, together with sodium chloride 9 mg/ml (0.9%) solution for infusion, should be administered according to current treatment guidelines.

Withdrawal symptoms
In patients who have received more than the physiological dose of hydrocortisone (approximately 40 mg cortisone or equivalent) for more than 3 weeks, withdrawal of treatment should be gradual. Dose reduction should be made depending largely on the disease being treated, the likelihood of relapse, as well as the dose of corticosteroid used. Clinical evaluation of the disease may be necessary during the withdrawal phase. If the likelihood of relapse is low, but there is uncertainty about suppression of the hypothalamic-pituitary-adrenal (HPA) axis, the dose of systemic corticosteroids may be rapidly reduced to physiological doses. Once a daily dose equivalent to 40 mg cortisone is reached, dose reduction should be slower to allow time for the HPA axis to recover.

In the following groups of patients, gradual withdrawal of systemic corticosteroid therapy should be considered even after courses of 3 weeks or less:

- Patients who have received several repeated courses of systemic corticosteroids, particularly if longer than 3 weeks;
- After a short course after one year of discontinuation of long-term treatment (months or years);
- Patients who have received systemic corticosteroid doses greater than 200 mg/day of cortisone (or equivalent);
- Patients who repeatedly take doses at night.

*Concomitant infections*
Corticosteroids can mask certain symptoms of an infection and new infections can occur during their use. Infections should not be more likely at a replacement dose of hydrocortisone, but the patient's clinical condition should during all infections be closely monitored and stress dosing of steroid initiated early (see section 4.2).

During transient illnesses such as low-grade infection, fever of any etiology, stressful situations such as minor surgical procedures, the daily replacement dose must be increased temporarily (see section 4.2, 'Use in intercurrent illness'). The patient must be carefully informed how to act in these situations and also advised to immediately seek medical attention should an acute deterioration occur; especially in cases of gastroenteritis, vomiting and/or diarrhea leading to fluid and salt loss, as well as to inadequate absorption of oral hydrocortisone.

Patients with adrenal insufficiency run the risk of a life-threatening adrenal crisis in the event of an infection; therefore, a strong clinical suspicion should exist with regard to infection and advice should be sought from a specialist in an early stage.

Patients with adrenal insufficiency and concomitant retroviral infection, such as HIV, need careful dose adjustment due to potential interaction with antiretroviral medicinal products and increased hydrocortisone dose due to the infection.

Scientific reports do not support immunosuppressive effects of hydrocortisone in doses that have been used for replacement therapy in patients with adrenal insufficiency. Therefore, there is no reason to believe that replacement doses of hydrocortisone will exacerbate any systemic infection or worsen the outcome of such an infection.

*Immunisation*
Corticosteroid replacement regimens for patients with adrenal insufficiency do not cause immunosuppression and administration of live vaccines is therefore not contraindicated.

*Undesirable effects of corticosteroid replacement therapy*
Most undesirable effects of corticosteroids are related to dose and duration of treatment. Undesirable effects are therefore less likely when using corticosteroids as replacement therapy.

*Using higher than normal doses of hydrocortisone*
High (supra-physiological) dosages of hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium.

Old age and low body mass index are known risk factors for common adverse reactions of pharmacological doses of glucocorticoids such as osteoporosis, thinning of skin, diabetes mellitus, hypertension and increased susceptibility to infections.

All glucocorticoids increase calcium excretion and reduce the bone-remodelling rate. Patients with adrenal insufficiency on long-term glucocorticoid replacement therapy have been found to have reduced bone mineral density.

Prolonged use of high doses of glucocorticoids may produce posterior subcapsular cataracts, and glaucoma with possible damage to the optic nerves. Such effects have not been reported in patients receiving replacement therapy with glucocorticoids in doses used in adrenal insufficiency.

Psychiatric adverse reactions may occur with systemic glucocorticoids. This may occur during commencement of treatment and during dose adjustments. Risks may be higher when high doses are given. Most reactions resolve after dose reduction, although specific treatment may be necessary.
Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

*Thyroid function*
Patients with adrenal insufficiency should be monitored for thyroid dysfunction as both hypothyroidism and hyperthyroidism may markedly influence the exposure of administered hydrocortisone.

Thyrotoxic Periodic Paralysis
Thyrotoxic Periodic Paralysis (TPP) can occur in patients with hyperthyroidism and with hydrocortisone-induced hypokalaemia. TPP must be suspected in patients treated with hydrocortisone presenting signs or symptoms of muscle weakness, especially in patients with hyperthyroidism.

If TPP is suspected, levels of blood potassium must be immediately monitored and adequately managed to ensure the restoration of normal levels of blood potassium.

*Insulin resistance*
Glucocorticosteroids can increase insulin resistance. The status of patients with diabetes mellitus should therefore be monitored. Patients with subclinical diabetes mellitus can develop clinical diabetes mellitus. A possible greater need for insulin or oral antidiabetics should be considered.

*Vision disturbances*
Vision disturbances can be reported with systemic and topical use of corticosteroids. If a patient develops symptoms such as blurred vision or other vision disturbances, consideration should be given to referring the patient to an ophthalmologist to assess the possible causes including cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) that have been reported after use of systemic and topical corticosteroids.
Regular ophthalmological monitoring for closed-angle glaucoma and glaucoma is highly desirable, especially during the initial phase of treatment.

*Paediatric population*
Corticosteroids used in doses above replacement therapy may cause growth retardation in infancy, childhood and adolescence; this may be irreversible. Treatment should be limited to the minimum dosage to minimise suppression of the hypothalamus-pituitary-adrenal axis and stunted growth. The growth and development of infants and children who undergo long-term corticosteroid therapy should be carefully monitored.

Bone mineral density may be impacted in children when higher doses of replacement steroids are used. The lowest appropriate dose of steroid according to the response of the individual patient should be used.

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.

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.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'

**4.5 Interaction with other medicinal products and other forms of interaction**

Hydrocortisone interactions listed below have been reported after therapeutic doses of glucocorticoids.

Potent CYP3A4 inducers, such as phenytoin, rifabutin, carbamazepine, oxcarbazepine, barbiturates (including phenobarbital and primidone), rifampicin, St. John's wort and less potent inducers such as the antiretroviral medicinal products efavirenz and nevirapine can accelerate the metabolic clearance of hydrocortisone, decrease terminal half-life and thus reduce circulating levels and increase fluctuations of cortisol (due to shorter terminal half-life). This may require dose adjustment of hydrocortisone.

It is expected that potent CYP3A4 inhibitors such as ketoconazole, itraconazole, posaconazole, voriconazole erythromycin, telithromycin, clarithromycin, ritonavir, grapefruit juice and liquorice can inhibit the metabolism of hydrocortisone, and thus increase blood levels. During long-term prophylactic treatment with any of the antibiotics, adjustment of the hydrocortisone dosage should be considered.

The effect of corticosteroids may be reduced for 3-4 days after treatment with mifepristone.

**4.6 Fertility, pregnancy and lactation**

Pregnancy
Hydrocortisone Hualan tablets can be used during pregnancy. There is no indication that hydrocortisone replacement therapy in pregnant women with adrenal insufficiency is associated with adverse outcome of the mother and/or the foetus. Untreated adrenal insufficiency during pregnancy is associated with poor outcome of both the mother and the foetus, therefore it is important to continue treatment during pregnancy.

Reproductive studies in animals have shown that glucocorticoids can cause foetal abnormalities and reproductive toxicity (see section 5.3).

The dose of hydrocortisone should be carefully monitored during pregnancy in women with adrenal insufficiency. Dosing according to individual clinical response is recommended.

Pregnant patients with fluid retention or pre-eclampsia should be closely monitored if they are administered corticosteroids.

Breast-feeding
Small quantities of corticosteroids are excreted in breast milk. Hydrocortisone Hualan tablets can be used during breast-feeding. Doses of hydrocortisone used for replacement therapy are unlikely to have any clinically significant impact on the child. Infants of mothers taking high doses of systemic glucocorticoids for prolonged periods may be at risk of adrenal suppression.

Fertility
It has been demonstrated that patients with adrenal insufficiency have reduced parity, which is most likely due to the underlying diseases, but there is no indication that hydrocortisone in doses for substitution therapy affects fertility. Corticosteroids may increase or decrease motility and number of spermatozoa in some patients.

**4.7 Effects on ability to drive and use machines**

Hydrocortisone Hualan tablets has minor influence on the ability to drive, to perform skilled tasks (e.g., riding bicycle) and use machines. Fatigue and dizziness have been reported.
Untreated and poorly replaced adrenal insufficiency may affect the ability to drive and use machines.

**4.8 Undesirable effects**

Summary of safety profile

Hydrocortisone is given as replacement therapy aimed at restoring normal cortisol levels. The adverse reaction profile in the treatment of adrenal insufficiency is therefore not comparable to that in other conditions requiring much higher doses of oral or parenteral glucocorticoids.

For properly dosed substitution therapy with hydrocortisone, the chance of the adverse effects listed below is slight. Overdosage over a longer period can lead to undesirable effects that are typical for glucocorticosteroids (such as Cushing syndrome) and can manifest itself in various forms. The incidence of the adverse effects below is not known. These are summarised below.

*Tabulated list of adverse reactions*

| *MedDRA - system organ class database* | *Adverse reactions (Frequency not known)* |
|---|---|
| Immune system disorders | Activation of infection (tuberculosis, fungal and viral infections including herpes) |
| Endocrine disorders | Induction of glucose intolerance or diabetes mellitus |
| Metabolism and nutrition disorders | Sodium and water retention and oedema tendency<br>Hypertension<br>Hypokalaemia |
| Psychiatric disorders | Euphoria<br>Insomnia<br>Psychosis with hallucinations and delirium<br>Mania |
| Eye disorders | Posterior subcapsular cataract<br>Glaucoma<br>Increased intraocular pressure<br>rarely: Blurred vision (see also section 4.4) |
| Cardiac disorders | Hypertrophic cardiomyopathy in prematurely born infants |
| Gastrointestinal disorders | Dyspepsia and deterioration of existing gastric ulcer<br>Nausea<br>Gastritis |
| Skin and subcutaneous tissue disorders | Cushing like symptoms, facial erythema, steroid acne, red striae, petechiae, ecchymoses, hirsutism<br>Disturbed wound healing |
| Musculoskeletal and connective tissue disorders | Osteoporosis with spontaneous fractures |
| Renal and urinary disorders | Potassium depletion with hypokalaemic alkalosis |
| Investigations | Weight increased |

Description of selected adverse reactions

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroids especially when a patient has a history of allergies to medicinal products.

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: Corticosteroids for systemic use, Glucocorticoids. 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

Corticosteroids in very high doses have been shown to be teratogenic in reproductive toxicity studies in mice. Mice that were exposed in utero had an increased incidence of cleft palate and growth retardation. In addition, there was an increased incidence of resorption.

## 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**

PA23341/001/004

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 14th June 2024

**10 DATE OF REVISION OF THE TEXT**

January 2026