

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg hydrocortisone.

Excipient(s) with known effect:

Each tablet contains 39.4 mg lactose monohydrate (equivalent to 37.4 mg lactose anhydrous).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

6.5 × 3.5 mm, white, oval, flat, bevelled with imprinted "H5" on one side and bisect on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Corticosteroid

- For use as replacement therapy in primary, secondary or acute adrenocortical insufficiency.
- 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 dose 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If the drug is to be stopped after more than a few days of treatment, it should be withdrawn gradually over a period of weeks to months, depending on dosage and duration of therapy.

In 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.

Use in the elderly: Steroids should be used cautiously in elderly patients, particularly if long term, since adverse events are enhanced in old age (see Section 4.4).

Method of administration

For oral administration.

4.3 Contraindications

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

Acute infectious processes: Patients with systemic infections (viral, fungal, bacterial, unless specific anti-infective therapy is employed (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

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 the 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 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.

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, muscular weakness, electrocardiographic changes, hypertension and untoward hormonal effects.

Corticosteroids should be used with caution in patients with hypothyroidism.

Hypertrophic cardiomyopathy

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.

Withdrawal symptoms

In patients who have received more than physiological doses of systemic corticosteroids (approximately 40 mg cortisone or equivalent) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about 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 3 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 3 weeks or less:

- patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks;
- when a short course has been prescribed within one year of cessation of long term therapy (months or years);
- patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy;
- patients receiving doses of systematic corticosteroid greater than 160 mg hydrocortisone;
- patients repeatedly taking doses in the evening.

Psychiatric adverse events

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.

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.

Paediatric population

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 (see section 4.2).

Use in the elderly

The common adverse events 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.

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 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.

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).

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

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

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

There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but it is usually resolved 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

There are some side effects associated with this product that may affect some patients' ability to drive and operate machinery. 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 incidence of predictable undesirable effects, including hypothalamic pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see section 4.4).

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

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:	
Not known	Leucocytosis, thromboembolism.
Immune system disorders:	
Not known	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).
Metabolism and nutrition disorders:	
Not known	Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis.
Psychiatric disorders:	
Common	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. *
Not known	Psychological dependence.
Nervous system disorders	
Not known	Insomnia and aggravation of schizophrenia. Increased intracranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy.
Eye disorders:	
Not known	Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.
Cardiac disorders:	
Not known	Myocardial rupture following recent myocardial infarction. Hypertrophic cardiomyopathy in prematurely born infants.
Gastrointestinal disorders:	
Not known	Dyspepsia, peptic ulceration with perforation and haemorrhage, abnormal distension, oesophageal ulceration, candidiasis, acute pancreatitis, nausea and malaise.
Skin and subcutaneous tissue disorders:	
Not known	Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, negative protein and calcium balance, and increased appetite, impaired healing, skin atrophy, bruising, striae, acne, telangiectasia
Musculoskeletal and connective tissue disorders:	
Not known	Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture.
Renal and urinary disorders:	

Not known	Suppression of the hypothalamo-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea.
General disorders and administration site conditions:	
Not known	Hypersensitivity, including anaphylaxis has been reported.
Investigations:	
Not known	Weight increased

*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 and psychological dependence has occurred; the frequency is not known.

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

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

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

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 gastrointestinal 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 gastrointestinal 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. These are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.

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

Lactose monohydrate
Maize starch
Silica, Colloidal Anhydrous
Povidone
Cellulose, Microcrystalline
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium foil blister packs containing 20, 30, 40, 50, 60, 70, 80, 90 or 100 tablets (each pack contains multiples of x10 tablet blister strips).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Renata Pharmaceuticals (Ireland) Limited, 12 Crowe Street, Dundalk, Co. Louth, Ireland, A91 NN29

8 MARKETING AUTHORISATION NUMBER

PA22865/003/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd February 2024

10 DATE OF REVISION OF THE TEXT

April 2024