SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone 10 mg Tablets

Genhyco 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg hydrocortisone.

Excipient(s) with known effect

Each tablet contains 191.6 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, oval shaped tablet of around 10.8 mm length and 7.0 mm width, engraved "HC10" on one side and a quarter score in the middle of the other side.

The tablet can be divided into equal halves or quarters.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy of adrenal insufficiency in adults, children and adolescents < 18 years of age.

4.2 Posology and method of administration

Posology

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

To simulate the normal diurnal rhythm of cortisol secretion, the first dose in the morning should be higher than the other doses.

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If the drug is to be stopped after more than a few days of treatment, it should be withdrawn gradually to avoid hypoadrenalism (see section 4.4).

Adults
A dosage of 15-30 mg a day, typically in two to three daily doses, is usually recommended. In patients with some remaining endogenous cortisol production a lower dose may be sufficient.

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.

Special populations

Paediatric population
Recommended replacement doses of hydrocortisone are 8-10 mg/m^2/day for patients with adrenal insufficiency alone and 10-15 mg/m^2/day in patients with congenital adrenal hyperplasia, typically in three or four divided doses.

In patients with some remaining endogenous cortisol production a lower dose may be sufficient.

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.

Elderly (≥ 65 years old)
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. In case of an age-related low body weight, it is recommended to monitor the clinical response as dose adjustment may be required.

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, see section 5.2.

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, see section 5.2.

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.

4.4 Special warnings and precautions for use

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

Adrenal 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. 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.

When a patient is vomiting or acutely unwell, parenteral hydrocortisone should be started without delay. The patient and one or more responsible family or household members should be trained in administering this in an emergency.

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.

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.

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.

Infections and immunisation

Replacement schedules of corticosteroids for people with adrenal insufficiency do not cause immunosuppression and therefore administration of live vaccines is not contraindicated.

Infection should not be more likely at a replacement dose of hydrocortisone, but all infections should be treated seriously and stress dosing of steroid initiated early (see section 4.2). Patients with adrenal insufficiency are at risk of life-threatening adrenal crisis during infection so clinical suspicion of infection should be high and specialist advice should be sought early.

Undesirable effects of corticosteroid replacement therapy

Most undesirable effects of corticosteroids are dose and duration of exposure related. Undesirable effects are therefore less likely when using corticosteroids as replacement therapy. In all patients suffering from adverse events under- and/or overdosing should be considered, and prescribers are encouraged to investigate the cause of the undesirable effects and increase or decrease the dose.

High (supra-physiological) dosages of hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Long-term treatment with higher than physiological hydrocortisone doses can lead to clinical features resembling Cushing’s syndrome with increased adiposity, abdominal obesity, hypertension and diabetes, and thus result in an increased risk of cardiovascular morbidity and mortality.

Patients should be warned of the signs of diabetes and the need to seek medical advice if they occur. All glucocorticoids increase calcium excretion and reduce the bone-remodelling rate. Long-term glucocorticoid replacement therapy may therefore reduce bone mineral density (see section 4.8). The lowest appropriate dose of steroid according to the response of the individual patient should be used.

Patients/and or carers should be warned that potentially severe psychiatric adverse reactions; euphoria, mania, psychosis with hallucinations and delirium have been seen in adult patients at replacement doses of hydrocortisone (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 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.

Corticosteroids may cause growth retardation in childhood and adolescence; this may be irreversible. Treatment should be limited to the minimum dose required to achieve desired clinical response and when reduction in dose is possible, the reduction should be gradual. Excessive weight gain with decreased height velocity or other symptoms or signs of Cushing syndrome indicate excessive glucocorticoid replacement. Children require frequent assessment to assess growth, blood pressure, and general well-being.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroids, especially when a patient has a history of allergies to medicinal products (see section 4.8).

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.

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.

Mineralocorticoid replacement
Treatment of primary adrenal insufficiency often warrants addition of a mineralocorticoid.

Excipients
This medicine 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

Pharmacokinetic interactions

Hydrocortisone is metabolised by cytochrome P450 3A4 (CYP3A4). Concomitant administration of medicinal products that are inhibitors or inducers of CYP3A4 may therefore lead to unwanted alterations in serum concentrations of hydrocortisone with the risk of adverse reactions, particularly adrenal crisis. The need for dose adjustment when such medicinal products are used can be anticipated and patients should be closely monitored.

Medicinal products inducing CYP3A4, requiring a potential increase in hydrocortisone dosing, include but are not limited to:

- Anticonvulsants: phenytoin, carbamazepine and oxcarbazepine
- Antibiotics: rifampicin and rifabutin
- Barbiturates including phenobarbital and primidone
- Antiretroviral medicinal products: efavirenz and nevirapine
- Herbal medicinal products such as St. John's Wort

Medicinal products/substances inhibiting CYP3A4, requiring a potential decrease in hydrocortisone dosing, include but are not limited to:

- Anti-fungals: itraconazole, posaconazole, voriconazole
- Antibiotics: erythromycin and clarithromycin
- Antiretroviral medicinal products: ritonavir
- Grapefruit juice
- Liquorice

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.

Pharmacodynamic interactions

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 is potentiation of the anticoagulation response to coumarins.

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 hypoprothrombinaemia. There is an increased risk of gastro-intestinal bleeding and ulceration when corticosteroids are given with acetylsalicylic acid and NSAIDs, although topical NSAIDs do not generally interact with corticosteroids. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

The desired actions of hypoglycaemic medicinal products including insulin are antagonised by corticosteroids.

4.6 Fertility, pregnancy and lactation

Pregnancy

Hydrocortisone 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.

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

Hydrocortisone crosses the placenta. Hydrocortisone is preferentially metabolised by placental 11βHSD2 to inactive cortisone reducing the foetal exposure.

Studies in animals have shown reproductive toxicity of corticosteroids (see section 5.3).

Breast-feeding

Hydrocortisone is excreted in breast milk. However, doses of hydrocortisone used for replacement therapy are unlikely to have any clinically significant impact on the child. Hydrocortisone for replacement therapy can be used during breast-feeding.

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 no or negligible influence on 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. Undesirable effects in adrenal insufficiency patients treated with physiological levels of hydrocortisone are mainly related to over- or under-dosing (see section 4.4).

Tabulated list of adverse reactions

The following adverse reactions have been reported in the scientific literature in adult patients for other hydrocortisone medicinal products when given as adrenal insufficiency replacement therapy with frequency not known (cannot be estimated from the available data).

MedDRA system organ class	Frequency: not known
Psychiatric disorders	Psychosis with hallucinations and delirium Mania Euphoria
Gastrointestinal disorders	Gastritis

	Nausea
Renal and urinary disorders	Hypokalaemic alkalosis

It is known that the use of glucocorticoids at higher doses and for indication other than replacement therapy for adrenal insufficiency can lead to the following side effects (frequencies not known):

Immune system disorders
Activation of an infection (tuberculosis, fungal and viral infections including herpes), hypersensitivity.

Endocrine disorders
Induction of glucose intolerance or diabetes mellitus.

Metabolism and nutrition disorders
Salt and water retention leading to oedema, hypertension, hypokalaemia.

Psychiatric disorders
Euphoria, psychosis, insomnia.

Eye disorders
Increased intraocular pressure and cataracts.

Gastrointestinal disorders
Dyspepsia and worsening of a pre-existing ulcer.

Skin and subcutaneous tissue disorders
Cushing-like symptoms, stretch marks, ecchymosis, acne and hirsutism, impaired wound healing.

Musculoskeletal and connective tissue disorders
Osteoporosis with spontaneous fractures and muscle weakness.

Paediatric population
Hydrocortisone has been used for more than 60 years in paediatrics with a safety profile similar to that in adults. Historical cohorts of adults treated from childhood for CAH have been found to have reduced bone mineral density and increased fracture rates and growth retardation (see section 4.4) - it is unclear if these relate to hydrocortisone therapy using current replacement regimens.

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 the Yellow Card Scheme, www.mhra.gov.uk/yellowcard or search for the MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Reports of acute toxicity and/or deaths following hydrocortisone overdose are rare. No antidote is available.

Treatment is probably not indicated for reactions due to chronic poisoning unless the patient has a condition that would render him/her unusually susceptible to ill effects

from hydrocortisone. 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.

Pharmacodynamic effects

Hydrocortisone is believed to be the principal corticosteroid secreted by the adrenal cortex. Naturally-occurring glucocorticoids (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/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 eliminated completely by metabolism by 11ßHSD type 1 and type 2 enzymes and CYP3A4 in the liver and in peripheral tissue to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol.

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

Special populations

Renal impairment
No studies have been conducted in patients with renal impairment. A small amount of cortisol is excreted in the urine unchanged (<0.5% of the daily production), meaning that cortisol is eliminated completely by metabolism. Since severe renal impairment may affect medicinal products completely eliminated via metabolism, dose adjustment may be needed.

Hepatic impairment
No study has been performed in patients with hepatic impairment, however data in the literature for hydrocortisone support that no dose adjustment is required in mild to moderate hepatic impairment. In case of severe hepatic impairment, the functional liver mass decreases and thus the metabolising capacity for hydrocortisone. This may require dose individualisation.

Paediatric population
No pharmacokinetic data are available in children or adolescents.

5.3 Preclinical safety data

Animal experiments have shown that prenatal exposure to very high doses of glucocorticoids can induce malformations (cleft palate, skeletal malformations). Animal studies have also shown that prenatal exposure to high doses of glucocorticoids (but lower than teratogenic doses) may be associated with increased risk of intrauterine growth retardation, cardiovascular disease in adulthood and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 5 years
HDPE container: 3 years

6.4 Special precautions for storage

Store in original package to protect from light.

6.5 Nature and contents of container

PVC/aluminium blister containing 30 or 100 tablets per carton.

HDPE container with HDPE cap (30’s count).
HDPE container with HDPE cap (100’s count).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Ltd
11 Boumpoulinas
1060 Nicosia, Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0155

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/11/2022

10 DATE OF REVISION OF THE TEXT

20/09/2023