AUSTRALIAN PRODUCT INFORMATION
ALKINDI® (hydrocortisone) - GRANULES (IN CAPSULE)

1 NAME OF THE MEDICINE

Hydrocortisone.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ALKINDI 0.5 mg granules in capsules for opening
Each capsule contains 0.5 mg hydrocortisone

ALKINDI 1 mg granules in capsules for opening
Each capsule contains 1 mg hydrocortisone

ALKINDI 2 mg granules in capsules for opening
Each capsule contains 2 mg hydrocortisone

ALKINDI 5 mg granules in capsules for opening
Each capsule contains 5 mg hydrocortisone

For the full list of excipients see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Granules in capsules for opening.

The granules are white to off-white and contained in a transparent colourless (size 00el) hard capsule.

ALKINDI 0.5 mg granules in capsules for opening
The capsule is printed with "INF-0.5" in red ink.

ALKINDI 1 mg granules in capsules for opening
The capsule is printed with "INF-1.0" in blue ink.

ALKINDI 2 mg granules in capsules for opening
The capsule is printed with "INF-2.0" in green ink.

ALKINDI 5 mg granules in capsules for opening
The capsule is printed with "INF-5.0" in grey ink

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Replacement therapy of adrenal insufficiency.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

ALKINDI was developed for use in patients requiring smaller doses. Alternative formulations of hydrocortisone should be considered for patients requiring larger doses.

Monitoring of the clinical response is necessary and patients should be observed closely for signs that might require dose adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual responsiveness to the medicinal product, and the effect of stress (e.g. surgery, infection, trauma). During stress it may be necessary to increase the dose temporarily.

Replacement therapy in primary and secondary adrenal insufficiency

ALKINDI is given as replacement therapy by oral administration of granules according to clinical practice, in a dose to be titrated against individual clinical response.

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 (CAH), typically in three or four divided doses.

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

In situations when the body is exposed to excessive physical and/or mental stress, patients may need an increased dose, especially in the afternoon or evening.

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 ALKINDI 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 ALKINDI.

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.

Changing from conventional oral glucocorticoid treatment to ALKINDI

When changing patients from conventional oral hydrocortisone replacement therapy (crushed, split or compounded) to ALKINDI, an identical total daily dose may be given. While no bioequivalence data to Australian hydrocortisone products exist, ALKINDI is therapeutically equivalent to conventional oral hydrocortisone formulations. As inaccuracy in the dosing with other oral hydrocortisone formulations (when crushed, split or compounded) is possible, changing a patient from other oral hydrocortisone formulations to ALKINDI can result in a relative fall in hydrocortisone exposure on the same nominal dose. This can lead to symptoms of adrenal insufficiency or crisis. Close monitoring of dose response and dose titration may be necessary when commencing ALKINDI.

Missed or incomplete dose

If a full dose of ALKINDI 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 the child receives two doses at the same time.

Patients and/or caregivers should be instructed to contact their healthcare professional if most of the granules in a dose are regurgitated, vomited or spat out, as a repeat dose may be required to avoid adrenal insufficiency.

Method of administration

The granules must be given orally and should not be chewed. The capsule shell must not be swallowed but carefully be opened as follows:

- The capsule is held so that the printed strength is at the top, and tapped to ensure all the granules are in the lower half of the capsule.
- The bottom of the capsule is gently squeezed.
- The top of the capsule is twisted off.
- The granules are either poured directly onto the child's tongue, or the granules are poured onto a spoon and placed in the child's mouth. For children who are able to take soft food, the granules may be sprinkled onto a spoonful of cold or room temperature soft food (such as yoghurt or fruit puree) and given immediately.
- Whichever method is used, the capsule is tapped to ensure all the granules are removed.

Immediately after administration a drink such as water, milk, breast-milk, or formula-milk should be given to help ensure all granules are swallowed.

If the granules are sprinkled onto a spoonful of soft food this should be given immediately (within 5 minutes) and not stored for future use.

The granules must not be added to liquid as this can result in less than the full dose being given, and may affect the taste masking which will allow the bitter taste of hydrocortisone to become apparent.

Do not administer via nasogastric tube as there is a risk of nasogastric tube blockage (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Detailed pictograms on how to administer the granules are provided in the Consumer Medicine Information.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 LIST OF EXCIPIENTS.
- Patients with dysphagia or premature infants where oral feeding has not been established.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Adrenal crisis

Where a child is vomiting or acutely unwell parenteral hydrocortisone should be started without delay, carers should be trained in adminstering this in an emergency.

Sudden discontinuation of therapy with hydrocortisone risks triggering an adrenal crisis and death. Medicinal product-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.

Adrenal crisis can occur when switching from conventional oral hydrocortisone formulations (crushed, split or compounded) to ALKINDI. Close monitoring of patients is recommended in the first week after the switch. Healthcare professionals should inform carers and patients that extra doses of ALKINDI should be given if symptoms of adrenal insufficiency are seen. If this is required, then an increase in the total daily dose of ALKINDI should be considered and immediate medical advice should be sought.

Immunisation

Replacement schedules of corticosteroids for people with adrenal insufficiency do not cause immunosuppression and are not, therefore, contraindications for administration of live vaccines.

Infections

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 DOSE AND METHOD OF ADMINISTRATION). 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.

Corticosteroids may cause growth retardation in infancy, 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. Infants require frequent assessment and should be evaluated at a minimum every 3 to 4 months to assess growth, blood pressure, and general well-being.

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS), 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.

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

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 which have been reported after use of systemic and topical corticosteroids.

Excretion of granules

The granules may sometimes be seen in stools since the centre of the granule is not absorbed in the gut after it has released the active substance. This does not mean the medicinal product has been ineffective and the patient should not take another dose for this reason.

Nasogastric tube feeding

ALKINDI granules are not suitable for nasogastric administration as they may cause tube blockage.

Use in the elderly

No data available.

Paediatric use

See section 5.1 PHARMACODYNAMIC PROPERTIES).

Effects on laboratory tests

See section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 ALKINDI 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 ALKINDI 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.

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No specific animal or clinical studies on the effects of hydrocortisone on fertility have been performed. Corticosteroids have been shown to impair fertility and reduce embryonic viability in studies in mice and rats.

Use in pregnancy (Category A)

Hydrocortisone for replacement therapy can be used during pregnancy. The ability of corticosteroids to cross the placenta varies between the different types of corticosteroids, however, hydrocortisone readily crosses the placenta.

Hydrocortisone and other corticosteroids have been shown to be teratogenic in animals. Abnormalities of fetal development observed following administration to pregnant animals include cleft palate, intrauterine growth retardation and effects on brain growth and development.

Use in lactation

Hydrocortisone for replacement therapy can be used during breast-feeding. Hydrocortisone is expected to be excreted in milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ALKINDI has no or negligible influence on the ability to perform skilled tasks (e.g. riding a bicycle) or using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

A total of 30 healthy (but dexamethasone-suppressed) adult male subjects in two phase 1 studies and 24 paediatric patients with adrenal insufficiency in two phase 3 studies have been treated with ALKINDI. There were no adverse reactions and no episodes of adrenal crisis seen in any of the studies.

In clinical practice most adverse reactions have been mild and self-limiting but adrenal crisis has been observed at time of changing from other hydrocortisone products and monitoring of patients at time of switch is advised (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Tabulated list of adverse reactions

The adverse reactions in Table 1 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).

Table 1. Adverse reactions

MedDRA System organ class	Frequency	Adverse reaction
Psychiatric disorders	Not known	Psychosis with hallucinations and delirium Mania Euphoria
Gastrointestinal disorders	Not known	Gastritis Nausea
Renal and urinary disorders	Not known	Hypokalaemic alkalosis

Description of selected adverse reactions

When changing a patient from other oral hydrocortisone formulations to ALKINDI, inaccuracy in the dosing possible with other oral hydrocortisone formulations can lead to a relative fall in hydrocortisone exposure on the same nominal dose, leading to symptoms of adrenal insufficiency such as tiredness, excessive sleeping, poor feeding, or adrenal crisis (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). It is unclear if these relate to hydrocortisone therapy using current replacement regimens.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 which case, symptomatic treatment should be instituted as necessary.

The biological half-life of hydrocortisone is about 100 minutes.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Corticosteroids for systemic use; glucocorticoids, ATC code: H02AB09.

Mechanism of action

Hydrocortisone is a glucocorticoid secreted by the adrenal cortex. The activity of the glucocorticoids is mediated by ubiquitously expressed glucocorticoid and mineralocorticoid receptors. Glucocorticoids have anti-inflammatory and immunosuppresive actions and salt-retaining properties. They affect the endocrine, cardiovascular, musculoskeletal and central nervous systems, as well as metabolism.

Clinical trials

Paediatric population

The pivotal study was an open-label single-dose single-centre trial in 24 paediatric patients aged less than 6 years requiring replacement therapy for adrenal insufficiency due to CAH, primary adrenal failure or hypopituitarism. The study consisted of three consecutive cohorts, the first including 12 patients aged 2 to less than 6 years, the second including 6 patients aged 28 days to less than 2 years, and the third including 6 neonates aged from birth to less than 28 days. This clinical study was performed in Europe, and patients were previously treated with European-sourced hydrocortisone.

Of these 24 patients, 23 had a diagnosis of CAH and 1 had a diagnosis of hypopituitarism including hypothyroidism. 1 patient had renal hypoplasia, 1 patient atopic dermatitis and 1 patient had rhinitis. The study used a single dose of ALKINDI granules equivalent to the previous morning's dose of each patient's usual glucocorticoid treatment. The ALKINDI dose range administered was 1 mg - 4 mg. Parents/carers (and where possible children) assessed the palatability of ALKINDI after administration using a 5-item Likert scale.

As this was a single-dose study, the primary efficacy assessment was serum cortisol at 60 minutes. In all 24 patients ALKINDI was found to increase cortisol values from baseline as expected: median baseline cortisol 14.1 nmol/L (range 14.1-104.5), median C_{max} 535.2 nmol/L (range 346.2-1445.1).

ALKINDI was positively assessed in terms of palatability. Among parents and carers asked about their child's experience of taking the medication (n=23), 82.6% agreed/strongly agreed that their child found swallowing ALKINDI easy. Six of the 12 children in Cohort 1 (age range 2.6 to 4.7 years) responded to an adjusted palatability questionnaire. ≥50% subjects reported that the taste, feel in mouth and ease of swallowing were very good and that they were likely to take the medicinal product again. 68.8% of healthy adult volunteers have described the taste as neutral.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, hydrocortisone is rapidly absorbed from the gastrointestinal tract and the oral ALKINDI 4x5 mg was approximately 87% bioavailable when compared to intravenous hydrocortisone in dexamethasone-suppressed healthy adult male volunteers.

The co-administration of ALKINDI with soft food (yoghurt and fruit puree) has been studied *in vitro* with no significant effect on dissolution seen.

Distribution

90% or more of circulating hydrocortisone 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.

Metabolism and excretion

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

The terminal half-life of hydrocortisone is about 1.5 hours following intravenous and oral dosing of hydrocortisone tablets and ALKINDI in dexamethasone-suppressed healthy adult male volunteers.

No studies have been conducted in patients with hepatic or renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Hydrocortisone was not mutagenic in bacteria. Positive results for clastogenicity have been reported for hydrocortisone *in vitro* (in cultured human lymphocytes) and *in vivo* (in mice), as with other steroid hormones.

Carcinogenicity

No adequate studies on the carcinogenic potential of hydrocortisone have been conducted in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Granules

Microcrystalline cellulose
Hypromellose
Magnesium stearate
Ethylcellulose

6.2 INCOMPATIBILITIES

See section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Prior to dispensing to the patient:

Store below 30°C.
Store in the original bottle in order to protect from light.

After dispensing:

Once opened, use within 60 days and store below 25°C.
Store in the original bottle in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

The capsules are provided in high-density polyethylene bottles with polypropylene closure with integrated desiccant.

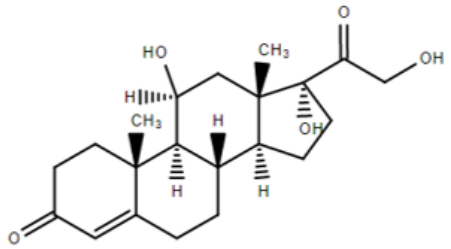
Pack sizes: 1 bottle containing 50 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Hydrocortisone

CAS number

50-23-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicines)

8 SPONSOR

Chiesi Australia Pty Ltd
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9 DATE OF FIRST APPROVAL

18 August 2020

10 DATE OF REVISION

05 February 2025

Summary table of changes

Section changed	Summary of new information
4.2	Addition of recommended management of missed or incomplete doses to avoid adrenal insufficiency
4.8	Addition of temporality of adverse reactions and additional information for adrenal crisis risk when changing a patient from other oral hydrocortisone formulations
8	Update Sponsor contact details
All	Minor editorial changes