New Medicine Assessment

Hydrocortisone Granules in Capsules for Opening (Alkindi®)

As Replacement Therapy of Adrenal Insufficiency in Infants, Children and Adolescents (< 18 Years Old)

Recommendation: AMBER0 for the treatment of infants and children (birth to < 18 years) with adrenal insufficiency receiving divided doses of < 5 mg for whom hydrocortisone must otherwise be individually prepared by manipulation such as by compounding (or crushing) or by production of special solutions in order to produce age-appropriate doses, or hydrocortisone given as off-label buccal tablets.

The dose of hydrocortisone and the patient's clinical condition should have been stabilised and reviewed prior to prescribing responsibility passing to primary care clinicians.

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

When recommending or handing over care, specialists should ask primary care prescribers to take over prescribing responsibility, and should give enough information about the indication, dose, monitoring requirements, use outside product licence and any necessary dose adjustments to allow them to confidently prescribe.

Summary of supporting evidence:

- Hydrocortisone tablets are not licensed for children and only available in 20 mg and 10 mg dose sizes, yet young children will only require between 4-10 mg per day, split into at least three doses, making accurate dosing difficult. Alkindi® is designed specifically for treating children with adrenal insufficiency and comes in the right doses for children of all ages. [2]
- The pharmaceutical form of Alkindi® capsules enable granules of the medicine to be sprinkled over soft food prior to administration. In addition, the granules are coated in a taste-masking film which masks the bitter taste of hydrocortisone and makes the formulation more palatable. [2]
- Alkindi® is significantly more expensive than hydrocortisone 10 mg tablets, particularly as the required daily dose increases.

Date: September 2021

Details of Review

Name of medicine (generic & brand name)**:** Hydrocortisone Granules in Capsules for Opening (Alkindi®)

Strength(s) and form(s): 0.5 mg, 1 mg, 2 mg, and 5 mg

Dose and administration: 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. [1]

BNF therapeutic class / mode of action: Glucocorticoids

Licensed indication(s): Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old).

Proposed use (if different from, or in addition to, licensed indication above): N/A

Course and cost:

For 50 pack sizes of Alkindi®

0.5 mg granules - £33.75

1 mg granules – £67.50

2 mg granules - £135

5 mg granules - £337.50

Assuming a dose of 8 to 15 mg/ m^2/day for a 6-year-old with a body surface area of 0.8 m^2, a

6.5 mg to 12 mg daily dose would be required resulting in an annual cost of **£3,194** to **£5,897** (figures taken from the Scottish Medicines Consortium (SMC) report). [2]

NB Drug tariff price has remained unchanged since the addition of Alkindi® in June 2019

Current standard of care/comparator therapies:

30 x Hydrocortisone 10 mg tablets = £3.82

Assuming the same dosing as above and c*osts for hydrocortisone 10mg tablets are based on using one tablet for each dose and assume wastage of the remainder of the tablet.*

3 to 4 tablets for 365 days = **£139** to **£185**

Relevant NICE guidance:

NICE Clinical Knowledge Summary - Addison's disease

Treatment regimens for Addison's disease are initiated and adjusted by a specialist endocrinologist.

Repeat prescriptions may be provided in primary care under a shared care arrangement.

Glucocorticoid replacement — hydrocortisone is usually used, but in specific circumstances

alternative forms of glucocorticoid (for example prednisolone) may be prescribed by endocrinology.

For children, daily dosage is usually around 8–10 mg/m^2 body surface area in three to four divided doses. [3]

Background and context

Adrenal insufficiency is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids. Due to the central role of these hormones in salt, and fluid homeostasis, adrenal insufficiency is a severe and potentially life-threatening condition. Primary adrenal insufficiency is rare with an estimated prevalence of 100 to 140 cases per million and an annual incidence of 4 per million. [4] The majority of cases of adrenal insufficiency in children are due to congenital adrenal hyperplasia, including 21-hydroxylase deficiency, and the incidence is estimated to range from 1 in 10,000 to 1 in 20,000 births. [5] In congenital adrenal hyperplasia, the pituitary gland compensates for the reduced cortisol formation by increasing the production of corticotrophin which in turn results in excessive adrenal androgen production. Immediate-release hydrocortisone is the standard of care in adrenal insufficiency and treatment prevents adrenal crisis and virilisation, allowing normal growth and development.

Hydrocortisone is the replacement therapy of choice in children and adolescents because it has lower potency and is shorter acting than prednisolone and dexamethasone and may have fewer adverse events. Oral hydrocortisone is currently available as immediate-release and modified-release tablets. For children who are unable to swallow tablets, current options include dividing or crushing immediate-release hydrocortisone 10mg tablets, specially formulated solutions or off-label use of buccal hydrocortisone tablets. Alkindi® is the first paediatric specific formulation of immediate-release hydrocortisone for replacement therapy of adrenal insufficiency in children and adolescents. [2] Alkindi® capsules were prioritised for review by LSCMMG following a request from East Lancashire CCG.

Summary of evidence

Summary of efficacy data in proposed use:

Since Alkindi® (granules in capsules for opening) is aimed to be bioequivalent to immediate-release hydrocortisone, its efficacy is expected to reflect that of standard hydrocortisone. [6] Therefore, to comply with the requirements of the European Medicines Agency paediatric investigation plan, the only study needed to evaluate efficacy in the target patient population was an open-label, single dose study in children less than 6 years of age requiring hydrocortisone replacement therapy for adrenal insufficiency due to congenital adrenal hyperplasia or hypopituitarism. [7]

Eligible patients had adrenal insufficiency confirmed by an inappropriately low cortisol level and were currently receiving hydrocortisone with or without fludrocortisone. They were enrolled into the study in consecutive cohorts defined by age: cohort 1 children aged 2 to <6 years; cohort 2 infants aged 28 days to <2 years and cohort 3 neonates aged 1 to <28 days. All patients received a single dose of Alkindi® equivalent to their current hydrocortisone dose (range 1mg to 4mg) under fasted conditions. Patients received Alkindi® at least 8 hours after their last dose of hydrocortisone and continued to receive their standard hydrocortisone treatment 8 hours after Alkindi®. Plasma sampling was performed 0, 60 and 240 minutes post-dose to centrally assess cortisol concentrations. [2] The primary endpoint of the study was met, with a statistically significant increase in serum cortisol levels observed at 60 minutes post Alkindi® dose compared to baseline serum cortisol levels with all subjects having cortisol levels above the clinically relevant limit at maximum Alkindi® plasma concentration levels. The results were also supported by secondary analyses. Cortisol levels at 4-hour post administration were lower than projected.

Palatability was assessed as a secondary endpoint. Palatability questionnaires showed that Alkindi® was positively received by healthy volunteers, parents/carers of paediatric subjects, and by the paediatric subjects themselves where subjects were old enough to respond to a specific questionnaire. It is of note that 95.5% of parents/carers would be happy to give their child Alkindi®

in the future and 95.5% preferred Alkindi® to the usual hydrocortisone medication. [6]

Summary of safety data:

Study Infacort-003 was of single-arm, single-dose design, therefore data on the adverse event profile are limited. A treatment-emergent adverse event was reported in 33% (8/24) of the overall study population; 33% (4/12) of patients in cohort 1; 33% (2/6) of patients in cohort 2 and 33% (2/6) of patients in cohort 3. Adverse events were mild in all patients except one patient who had moderately severe events (vomiting and fatigue) and there were no treatment-related adverse events. The most commonly reported adverse events were diarrhoea (12% [3/24]), vomiting (8.3% [2/24]) and rash (8.3% [2/24]). [2]

The EPAR for Alkindi® concludes that the safety profile of Alkindi®, in the low number of patients included in Infacort 003, was in line with the historical experience with immediate release hydrocortisone. No choking events were reported to the EMA. [6]

The adverse reactions listed in the SPC for Alkindi® are tabulated below [1]:

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

Alkindi® is contraindicated in patients with dysphagia or premature infants where oral feeding has not been established. The SPC also contains warnings about visual disturbances being reported with systemic corticosteroids. The SPC warns against using Alkindi® granules in nasogastric tubes. The SPC also warns that granules may be visible in stools and this does not mean that the medicinal product has been ineffective.

The Medicines and Healthcare products Regulatory Agency (MHRA) published a drug safety update warning of the risk of acute adrenal insufficiency in children when switching from hydrocortisone tablet formulations to granules. . [8]

Strengths and limitations of the evidence:

Strengths

- Hydrocortisone tablets are not licensed for children and only available in 20mg and 10mg dose sizes, yet young children will only require between 4-10mg per day, split into at least 3 doses, making accurate dosing difficult. Alkindi® is designed specifically for treating children with adrenal insufficiency and comes in the right doses for children of all ages. [2]
- The pharmaceutical form of Alkindi® capsules enable granules of the medicine to be sprinkled over soft food prior to administration. In addition, the granules are coated in a taste-masking film which masks the bitter taste of hydrocortisone and makes the formulation more palatable. [2]

- The EMA concluded that Alkindi® is therapeutically bioequivalent to the reference product for hydrocortisone (10 mg tablets).

Limitations

- The MHRA have published safety advice relating to the risk of acute adrenal insufficiency when switching to Alkindi®.
- Alkindi® is significantly more expensive than hydrocortisone 10 mg tablets, and cost differences are more marked as the required daily dose increases.
- The Scottish Medicines Consortium (SMC) only recommends Alkindi® for use dependent upon a Patient Access Scheme that improves the cost effectiveness of Alkindi®.

Summary of evidence on cost effectiveness:

The Scottish Medicines Consortium (SMC) carried out an economic analysis of Alkindi®. Key findings are summarised in the tables below:

Table 1 - Base case results

Comparator	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio ICER
Standard of care (SoC)	£3,662	0.16	£23,373

Table 2 - Key scenario analysis results

Scenario analysis	**ICER**
Daily hydrocortisone dose of 15mg/m^2	£65,252
Time horizon 40 years	£31,426
SoC assuming higher buccal use	£28,844
RR of one for crises	£41,363
RR of one for diabetes	£24,277
RR of one for growth	£30,669
RR of one for BMI (obesity)	£32,389
Baseline HRQoL gain for caregivers of 0.05	£9,496
Risk reduction for adrenal/hypoglycaemic crisis only	£55,449
Two hydrocortisone tablets required per day	£42,459
Two hydrocortisone tablets and risk reduction for adrenal/hypoglycaemia crisis only	£101,952

Prescribing and risk management issues:

MHRA Drug Safety Update

When changing patients from conventional oral hydrocortisone replacement therapy to Alkindi, an identical total daily dose may be given. Alkindi is therapeutically equivalent to conventional hydrocortisone tablets.

If a child is switching to Alkindi granules, parents or carers should be advised to carefully observe the child during the first week for symptoms of adrenal insufficiency, such as tiredness,

floppiness, unstable temperature, headache and vomiting

Parents or carers should be counselled on what to do if the child develops symptoms of adrenal insufficiency, including the need to seek immediate medical advice and administer extra doses of Alkindi if appropriate

If a child requires additional doses during the first week after switching to Alkindi, a long-term increase in the daily dose of Alkindi should be considered. [8]

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. [1]

Commissioning considerations:

Innovation, need and equity implications of the intervention:

For adrenal insufficiency, young children will only require between 4-10mg of hydrocortisone per day, split into at least 3 doses, making accurate dosing difficult. Alkindi® is the only licensed treatment in paediatric patients and is designed specifically for treating children with this adrenal insufficiency and comes in the right doses for children of all ages. Alkindi® will provide accurate dosing (particularly for children) making life easier for parents/carers to administer doses and potentially preventing unwanted side effects due to inaccurate dosing. It is produced as tiny granules enabling infants to swallow safely (suitable from birth). It also has a taste masking coating so is palatable, whereas the current tablets are very bitter tasting. [2]

Financial implications of the intervention:

Extrapolating from the assumptions considered in the SMC review of Alkindi®, 7 patients would be eligible for treatment each year in Lancashire and South Cumbria.

For Alkindi® capsules:

Assuming a dose of 8 to 15 mg/ m^2/day for a 6-year-old with a body surface area of 0.8 m^2, a

6.5 mg to 12 mg daily dose would be required resulting in an annual cost of **£3,194** to **£5,897**.

The total annual cost to treat 7 patients is **£22,358** to **£41,279**

For hydrocortisone 10 mg tablets:

Assuming the same dosing as above and c*osts for hydrocortisone 10mg tablets are based on using one tablet for each dose and assume wastage of the remainder of the tablet.*

3 to 4 tablets for 365 days = **£139** to **£185**

The total annual cost to treat 7 patients is **£973** to **£1,295**

This would lead to a potential cost burden to the Lancashire and South Cumbria health economy of **£21,385** to **£39,984**.

Service Impact Issues Identified:

No service impact issues are expected for the supply of Alkindi® capsules. Patients would continue to be initiated on treatment by specialists before prescribing responsibility is passed over

to primary care clinicians.
Equality and Inclusion Issues Identified:
No Equality issues are anticipated as this is an additional formulation of an existing treatment.
Cross Border Issues Identified:
Hydrocortisone granules are “Green following specialist initiation” according to the GMMMG formulary and should only be used in patients requiring doses less than 5 mg. Alkindi® should not be used in combination with hydrocortisone tablets to make up dose of increments more than 5 mg. In Pan Mersey hydrocortisone granules are “Amber Initiated” meaning that prescribing is the responsibility of the specialist until the dose is stabilised and reviewed.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics Alkindi 0.5 mg granules for opening," Diurnal Ltd, February 2018. [Online]. [Accessed March 2021].

[2] Scottish Medicines Consortium, "Hydrocortisone 0.5 mg, 1 mg, 2 mg and 5 mg granules in capsules for opening (Alkindi)," 7 September 2018. [Online]. Available: https://www.scottishmedicines.org.uk/media/3758/hydrocortisone-granules-alkindi-final-september-2018-for-website.pdf. [Accessed March 2021].

[3] National Institute of Health and Care Excellence, "Clinical Knowledge Summary - Addison's Disease," December 2020. [Online]. Available: https://cks.nice.org.uk/topics/addisons-disease/. [Accessed March 2021].

[4] SR Bornstein et al , "Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline," *Journal Clin Endocrinol Metab,* vol. 101, no. 2, pp. 364-389, 2016.

[5] PW Speiser et al, "Congenital Adrenal Hyperplasia due to Steroid 21 - Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline," *J Clin Endocrinol Metab,* vol. 95, no. 9, pp. 4133-4160,

2010.

[6] European Medicines Agency, "Public Assessment Report Alkindi EMEA/H/C/004416/0000," December 2017. [Online]. Available: https://www.ema.europa.eu/en/documents/assessment-report/alkindi-epar-public-assessment-report_en.pdf. [Accessed March 2021].

[7] U Neumann et al, "Absorption and tolerability of taste-masked hydrocortisone granules in neonates, infants and children under 6 years of age with adrenal insufficiency," *Clinical Endocrinology,* vol. 88, pp. 21-29, 2018.

[8] Medicines and Healthcare products Regulatory Agency, "Alkindi (hydrocortisone granules): risk of acute adrenal insufficiency in children when switching from hydrocortisone tablet formulations to granules," February 2021. [Online]. Available: https://www.gov.uk/drug-safety-update/alkindi-hydrocortisone-granules-risk-of-acute-adrenal-insufficiency-in-children-when-switching-from-hydrocortisone-tablet-formulations-to-granules#new-safety-advice-to-parents-or-carers. [Accessed March 2021].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Date: September 2021