

hydrocortisone 0.5mg, 1mg, 2mg and 5mg granules in capsules for opening  
(Alkindi®) SMC2088

**Diurnal Limited**

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarized as follows:

**ADVICE:** following a full submission

**hydrocortisone (Alkindi®)** is accepted for restricted use within NHSScotland.

**Indication under review:** replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to <18 years old).

**SMC restriction:** for the first-line treatment of infants and young children with adrenal insufficiency aged from birth to less than six years of age 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.

In a single-dose, single-arm, phase III study in children aged <6 years with adrenal insufficiency, Alkindi® significantly increased plasma cortisol levels at 60 minutes compared with baseline.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of Alkindi®. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower

**Chairman**  
**Scottish Medicines Consortium**

## Indication

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

## Dosing Information

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 to 10mg/m<sup>2</sup>/day for patients with adrenal insufficiency alone and 10 to 15mg/m<sup>2</sup>/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.

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.

The capsule shell must not be swallowed but carefully be opened. The granules must be given orally and should not be chewed. The granules are either poured directly onto the child's tongue, or 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 (within five minutes). Immediately after administration a drink such as water, milk, breast-milk or formula-milk should be given to help ensure all granules are swallowed. 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.

The summary of product characteristics (SPC) also gives recommendations for treatment pre-operatively, during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenal reserve.<sup>1</sup>

## Product availability date

3 September 2018

Alkindi® meets SMC ultra-orphan criteria.

## Summary of evidence on comparative efficacy

Adrenal insufficiency is caused by inability of the adrenal cortex to produce cortisol and in children the majority of cases are due to congenital adrenal hyperplasia. Treatment involves replacement glucocorticoid therapy (usually with hydrocortisone). Hydrocortisone granules in capsules for opening, hereafter referred to as Alkindi®, is a new formulation of immediate-release hydrocortisone for replacement therapy of adrenal insufficiency in children and adolescents.<sup>1, 2</sup> The submitting company has requested that SMC considers the use of Alkindi® for a subpopulation of the licensed indication: for the first-line treatment of infants and young children with adrenal insufficiency aged from birth to less than six years of age 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 pivotal evidence comes from an open-label, single-dose, single-arm, phase III study (Infacort-003) performed in patients aged less than 6 years requiring hydrocortisone replacement therapy for adrenal insufficiency due to congenital adrenal hyperplasia or hypopituitarism. 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.

The primary outcome was the maximum cortisol concentration in the serum up to 240 minutes post-dose.<sup>2,3</sup> At 60 minutes, the mean cortisol concentration was significantly higher than baseline in the full study population ( $p < 0.0001$ ). Based on the 1% alpha level, the mean cortisol level was also significantly increased from baseline in cohort 1, but not in cohorts 2 or 3. The second sampling time point at 240 minutes was thought to be the best predictor of area under the curve (AUC). At 240 minutes, the mean cortisol concentration was significantly higher than baseline in the full study population ( $p < 0.0026$ ) and in cohort 1 ( $p = 0.0005$ ) but not in cohorts 2 or 3. As detailed in table 1 below, not all patients had a cortisol level at 240 minutes that was higher than baseline.<sup>2</sup>

**Table 1:** Primary outcome: maximum change in serum cortisol levels up to 240 minutes post-dose, based on samples taken at 0, 60 and 240 minutes.<sup>2-4</sup>

	<b>Absolute geometric mean (standard deviation serum cortisol levels; nanomol/L)</b>			
	<b>All patients (n=24)</b>	<b>Cohort 1 (n=12)</b>	<b>Cohort 2 (n=6)</b>	<b>Cohort 3 (n=6)</b>
<b>Baseline</b>	22.71 (23.85)	25.96 (13.42)	28.00 (41.84)	14.10 (0.00)
<b>60 minutes; p-value versus baseline</b>	575.77 (299.53) $p < 0.0001$	547.13 (82.90) $p = 0.0005$	450.10 (88.93) $p = \text{NS}$	815.71 (473.88) $p = \text{NS}$
<b>240 minutes; p-value versus baseline</b>	60.07 (100.40) $p = 0.0026$	58.72 (30.58)	70.74 (55.28) $p = \text{NS}$	55.64 (194.99) $p = \text{NS}$
	<b>Number (%) of patients with cortisol levels above baseline</b>			
<b>60 minutes; p-value versus baseline</b>	24 (100%) $p < 0.0001$	12 (100%) $p = 0.0005$	6 (100%) $p = \text{NS}$	6 (100%) $p = \text{NS}$
<b>240 minutes; p-value versus baseline</b>	19 (83%) $p = 0.0026$	12 (100%) $p = 0.0005$	2 (40%) $p = \text{NS}$	5 (83%) $p = \text{NS}$

NS= not significant was based on a 1% alpha level (ie  $p < 0.01$ ).

The secondary outcome was an assessment of palatability which found that:<sup>2-4</sup>

- 83% (19/23) of parents and carers agreed or strongly agreed that their child found swallowing Alkindi® easy
- 65% (15/23) agreed or strongly agreed that their child showed a positive reaction after Alkindi® administration
- 95% would be happy to give their child Alkindi® in the future
- 95% would prefer Alkindi® for their child's treatment compared with their usual hydrocortisone formulation.

The study was followed by an open-label extension (Infacort-004) in which patients could continue to receive long-term Alkindi®. It was designed primarily to assess the longer term safety of Alkindi® but growth velocity, cortisol levels were measured as secondary outcomes.<sup>5</sup> Eighteen of the 24 patients in Infacort-003 entered Infacort-004. The study is ongoing.<sup>6</sup>

Alkindi® was found to be therapeutically equivalent to immediate-release hydrocortisone tablets in two bioequivalence studies in healthy adults.<sup>1, 2</sup>

Other data were also assessed but remain commercially confidential.\*

## Summary of evidence on comparative safety

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]).<sup>2, 3</sup>

The European public assessment report (EPAR) notes that the risk of choking with Alkindi® granules is assumed to be negligible and certainly much less than that associated with the current treatment practice of administering crushed tablets. There were no choking events reported in the Infacort-003 and 004 studies.<sup>2</sup>

The safety profile of Alkindi®, in the small number of patients treated in Infacort-003, was considered by the European Medicines Agency (EMA) to be in line with historical experience with immediate release hydrocortisone.<sup>2</sup>

Other data were also assessed but remain commercially confidential.\*

## Summary of clinical effectiveness issues

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.<sup>9</sup> 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. 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.<sup>10</sup> 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.<sup>2, 9-11</sup> 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. Clinical experts consulted by SMC consider there is unmet need in this therapeutic area due to the lack of a licensed preparation. Alkindi<sup>®</sup> is the first paediatric specific formulation of immediate-release hydrocortisone for replacement therapy of adrenal insufficiency in children and adolescents. Alkindi<sup>®</sup> meets SMC ultra-orphan criteria.

The submitting company has requested that SMC considers the use of Alkindi<sup>®</sup> for a subpopulation of the licensed indication: for the first-line treatment of infants and young children with adrenal insufficiency aged from birth to less than six years of age for whom hydrocortisone must 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 EMA approved Alkindi<sup>®</sup> on a paediatric use marketing authorisation (PUMA), granted for a medicine already authorised, but no longer under patent protection, and developed specifically for children. This was based on a paediatric investigation plan (PIP) which was approved by the EMA's Paediatric Committee. Therefore, in line with the PIP, the efficacy and safety data for Alkindi<sup>®</sup> are limited to bioequivalence studies with the available tablet formulation in healthy adults and the single-dose, single-arm pharmacokinetic and palatability phase III study (Infacort-003) in 24 children <6 years.<sup>2</sup>

The primary outcome in Infacort-003 of maximum cortisol levels was statistically significantly greater at 60 minutes than baseline in the full study population and in cohort 1 but not in cohorts 2 or 3. However, the study was not powered to detect a difference in the individual cohorts.<sup>2, 3</sup> The EPAR notes that peak cortisol levels (in healthy adults) of 400 to 1,000 nanomol/L at 60 minutes post-dose and of 100 to 300 nanomol/L at 4 hours post-dose were expected to be associated with optimal replacement therapy. However the maximum concentration in Infacort-003 may reflect the sampling time (60 minutes) rather than the true maximum concentration. At the 240 minutes sampling time point, the cortisol levels were lower than expected and in some patients the cortisol level was lower than at baseline. However there were no subsequent concerns with efficacy in the longer-term Infacort-004 study.<sup>2</sup>

Results from the Infacort-003 study indicated that patients generally found the formulation to be palatable. However it is unclear how assessment based on a single dose would extrapolate to longer-term treatment. In addition, the questionnaire used to assess palatability was developed by the submitting company and its validity has not been established.<sup>2, 3</sup>

The study population was aged <6 years and this represents the positioning proposed by the submitting company. The marketing authorisation includes the treatment of patients <18 years and this was based on a PIP plan waiver for the population of patients aged from 6 years to less than 18 years.<sup>2</sup> All patients in Infacort-003 had a diagnosis of congenital adrenal hyperplasia, except for one patient who had hypopituitarism. However in children, congenital adrenal hyperplasia is considered to be the most common cause of adrenal insufficiency.

The EPAR notes that Alkindi<sup>®</sup> has not been studied in preterm infants with adrenal insufficiency and caution is recommended in treating this age group.<sup>2</sup> The SPC notes that Alkindi<sup>®</sup> is contra-indicated in premature infants where oral feeding has not been established.<sup>1</sup>

There are no data comparing Alkindi® directly or indirectly with alternative formulations of hydrocortisone. The economic analysis is based on responses from a Delphi Panel and the results of the pivotal study were not used in the economic analysis.

The introduction of Alkindi® would offer the advantage of an available formulation that is more suitable for administration to paediatric patients than currently available options (eg dividing or crushing 10mg tablets). The available dosage range (0.5mg, 1mg, 2mg and 5mg) should ensure more precise dosing, clinical experts consulted by SMC consider the place in therapy for Alkindi® is to reduce the risk of under or over dosing with currently available formulations. In addition, the granules are coated in a taste-masking film which masks the bitter taste of hydrocortisone and makes the formulation more palatable.

## Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing Alkindi® (hydrocortisone granules in capsules) with standard of care (SoC) as replacement therapy for adrenal insufficiency in infants and children aged <6 years old. This reflects the selective positioning sought by the company as the license covers treatment up to age <18 years. SoC consisted of other formulations of hydrocortisone, the mix assumed being tablets (90% patients), solution (5% patients) and buccal tablets (5% of patients) based on clinical opinion. SMC clinical expert feedback indicates this comparator mix is reasonable.

The bioequivalence of Alkindi® with hydrocortisone tablets has been established in clinical studies. The premise of the economic analysis is that there are quality of life and mortality reduction benefits from co-morbidity risk reduction from the ability of Alkindi® to deliver accurate and consistent dosing in young children aged up to 6 years who need only small doses of hydrocortisone. In contrast, hydrocortisone tablets are only available at a minimum dose of 10mg, and so need to be quartered and dissolved/crushed to try and provide the appropriate dose, which leads to inaccuracies and higher risk of co-morbidities. The four co-morbidities considered were adrenal or hypoglycaemic crisis, diabetes, growth restriction, and obesity (measured by BMI). The economic model consisted of a sub-model for each co-morbidity whereby baseline mortality was estimated for adrenal/hypoglycaemic crisis and diabetes, and health related quality of life impact (in the form of a utility decrement) for all co-morbidities was estimated based on published studies, primarily in congenital adrenal hyperplasia (CAH), and via clinical opinion. A 'relative risk reduction in each co-morbidity for more accurate and consistent dosing of Alkindi® versus SoC was then applied

The benefit of accurate and consistent dosing on reducing the risk of each co-morbidity was estimated through a Delphi Panel of 14 European clinicians (three from the UK) who were asked to estimate the improvement on a scale of 0-100%, the average of which was then directly converted to a 'relative risk' (RR) for Alkindi® vs SoC. From this process the RRs used to represent the treatment effect of Alkindi® vs SoC in each co-morbidity sub-model were 0.46 for crises, 0.59 for diabetes, 0.40 for height, and 0.51 for weight. A 0.016 probability of death from adrenal/hypoglycaemic crisis was also included based on the Delphi panel feedback, and mortality risk from diabetes from a published source was included in the analysis<sup>7</sup>. It was assumed that the treatment effect would only apply whilst patients were on treatment with Alkindi® i.e. up to age 6, after which patients were assumed to switch to SoC hydrocortisone for the rest of the time horizon.

Age adjusted utility decrements for each co-morbidity were estimated from published studies in diabetes, or BMI and height relationships with utility in the UK general population. A utility decrement was estimated for adrenal crisis using the disutility of a hypoglycaemia episode in diabetes as a proxy. Health related quality of life (HRQoL) impact of loss of height and increasing BMI were only applied in the economic analysis from age 18 as the utility decrements were derived from studies in the adult general population. No disutilities or costs associated with adverse events were included in the

economic analysis as the Alkindi® safety profile was similar to the other hydrocortisone formulations.

Treatment duration with Alkindi® was from a starting age of 1 year (assumed to be the average age of diagnosis based on a published study in the UK)<sup>8</sup> to age 6, and account was taken of a lower relative adherence to hydrocortisone in the SoC patients, with an estimate of 67% reduction in non-adherence with Alkindi® applied based on clinical expert feedback.

Medicine acquisition costs were included, but no medicine administration costs were assumed for each hydrocortisone formulation. The cost of Alkindi® and SoC hydrocortisone was based on an assumed dose of 10mg/m<sup>2</sup> as recommended in clinical guidelines in adrenal insufficiency, and the cost of Alkindi® based on this dose multiplied by an estimated BSA for each age of patient from 0-5 years, administered three times daily. The cost of hydrocortisone tablets (the primary formulation in SoC) was based on an assumption that whilst patients would attempt to divide each 10mg tablet that is available into the appropriate dose required according to patient age, a whole 10mg tablet would be used for each of the three daily doses. This was justified by the company to be in line with guidance from the Royal Pharmaceutical Society and the US Food and Drug Administration that compounded doses should be taken by the patient as soon as possible to reduce the risk of degradation and minimise safety risks.

Adrenal insufficiency monitoring costs consisting of a set of visits to health professionals estimated by expert clinical opinion (3 UK clinicians in the Delphi Panel), and use of concomitant medications were included, but assumed in the base case to be the same for Alkindi® and SoC. In addition, co-morbidity costs were estimated based on resource use estimates from clinical experts for an adrenal crisis, and published estimates of the cost of diabetes.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

**Table 2: Base case results (without PAS for Alkindi®)**

Comparator	Incremental Cost	Incremental QALY	ICER
SoC	£3,662	0.16	£23,373

QALYs = quality-adjusted life-years, ICER = incremental cost-effectiveness ratio

**Table 3: Key scenario Analysis results (without PAS for Alkindi®)**

Scenario analysis	ICER without PAS
Daily hydrocortisone dose of 15mg/m <sup>2</sup>	£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

ICER = incremental cost-effectiveness ratio

The main weaknesses in the economic analysis were as follows:

- The estimation of Alkindi® treatment effect ('relative risks' for Alkindi® vs SoC hydrocortisone formulations for each co-morbidity) are not based on any direct evidence from the Alkindi® clinical studies but are estimated using clinical expert opinion, hence are speculative and associated with high uncertainty. The relative risk estimates used in the economic analysis based on achieving more accurate dosing seem large, so there are face validity concerns. There are also apparent weaknesses in the way the Delphi Panel questions were asked without a clear comparator reference point regarding the estimated risk reduction or improvement in each co-morbidity. Overall, the estimation of short and long term HRQoL gain and mortality reduction associated with more accurate Alkindi® dosing in 0-5 year olds extrapolated over a lifetime horizon appear optimistic. Scenarios assuming more pessimistic assumptions regarding the risk reduction of long term co-morbidities associated with Alkindi® dosing advantages were requested from the company, the least favourable of which demonstrated an estimated QALY gain of 0.06 for a scenario in which the only risk reduction was in adrenal/hypoglycaemic crisis.
- The company assumption of the use of three hydrocortisone 10mg tablets may not be representative of clinical practice, especially as the maximum daily dose that appears to be needed for a 5 year old is 7.6mg (therefore could theoretically be met through one compounded tablet). SMC clinical experts suggested that the extent of patient re-use of compounded tablets within one day is variable but this is not considered to be best practice. The SMC committee considered however the most relevant comparison for Alkindi® in younger patients requiring small doses would be with best practice of using full hydrocortisone tablets for each administration.

The Committee also considered the benefits of Alkindi® in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as Alkindi® is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and after application of the appropriate SMC modifiers, the Committee accepted Alkindi® for restricted use in NHS Scotland.

Other data were also assessed but remain commercially confidential.\*

## Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received a patient group submission from The Pituitary Foundation and a joint submission from The Congenital Adrenal Hyperplasia (CAH) Support Group and the Addison's Disease Self-Help Group. All three organisations are registered charities.
- The Pituitary Foundation has received 11.9% pharmaceutical company funding in the past two years, including from the submitting company. The CAH Support Group has not received any funding from pharmaceutical companies in the past two years. The Addison's Disease Self-Help Group has received 17% pharmaceutical company funding in the past year, with none from the submitting company.
- Adrenal Insufficiency often affects a patient's daily life, most notably due to tiredness and fatigue. Adrenal Insufficiency is associated with increased morbidity and mortality compared with the general population, and patients require life-long treatment. Avoiding an adrenal crisis requires careful management and has a significant effect on the day-to-day lives of patients and carers. This management is significantly more complicated when patients are children.
- Getting the hydrocortisone dose titrated to children's needs is essential, not only to keep them well and out of hospital but to ensure their growth and weight is kept steady. Currently the tablets available are not licensed for children and come 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 this condition 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 which even a new-born baby can swallow safely. It also has a taste masking coating so is palatable, whereas the current tablets are very bitter tasting.

## Additional information: guidelines and protocols

The Scottish Paediatric Endocrine Group (SPEG) Managed Clinical Network (MCN) published guidance entitled the Secondary care management of suspected adrenal crisis in children and young people in 2015.<sup>12</sup> This guidance was updated in June 2017 and makes the following recommendations regarding maintenance steroid replacement using hydrocortisone:

- The physiological replacement dose of hydrocortisone for children is 10mg/m<sup>2</sup>/day. This is given three times daily, with the largest dose given in the morning. Although some children may require hydrocortisone replacement four times daily.
- Families should know how to increase the dose of hydrocortisone during illness. The normal sick day dose is double the daytime dose given three times daily.<sup>12</sup>

The National Institute for Health and Care Excellence (NICE) published a Clinical Knowledge Summary (CKS) on Addison’s disease in March 2016.<sup>13</sup> The CKS states that glucocorticoid and mineralocorticoid replacement are needed, but androgen replacement is not routinely prescribed in the UK. The following recommendations regarding glucocorticoid replacement in children are made:

- Hydrocortisone is usually used, but longer-acting glucocorticoids, such as prednisolone and dexamethasone, are sometimes used to avoid the peaks and troughs which may occur with hydrocortisone.
- Dosages in children are usually in the region of 8–10 mg/m<sup>2</sup> daily in three divided doses, although the total daily dose may be divided into a larger morning dose and a smaller evening dose.<sup>13</sup>

The US Endocrine Society published the clinical practice guideline Diagnosis and treatment of primary adrenal insufficiency in 2016.<sup>9</sup> This guidance recommends that:

- In children with primary adrenal insufficiency, treatment with hydrocortisone in three or four divided doses (total starting daily dose of 8 mg/m<sup>2</sup> body surface area) over other types of glucocorticoid replacement therapies, with doses adjusted according to individual need.
- In children with primary adrenal insufficiency, avoid synthetic, long-acting glucocorticoids (eg, prednisolone, dexamethasone).
- monitoring glucocorticoid replacement by clinical assessment, including growth velocity, body weight, blood pressure, and energy levels.<sup>9</sup>

## Additional information: comparators

Hydrocortisone immediate release tablets.

## Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Alkindi®	8 to 15mg/m <sup>2</sup> /day in three to four divided doses (ie 6.5mg to 12mg daily)	3,194 to 5,897
Hydrocortisone 10mg tablets	8 to 15mg/m <sup>2</sup> /day in three to four divided doses	1,239

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 11 June 2018 for hydrocortisone tablets and from MIMS online on 5 September 2018 for Alkindi®. Costs are based on assumptions for a 6 year old child, weighing 20kg, with a body surface area of 0.8m<sup>2</sup>. Costs for hydrocortisone 10mg tablets are based on using one tablet for each dose and assume wastage of the remainder of the tablet. Costs do not take any patient access schemes into consideration.*

## **Additional information: budget impact**

The submitting company estimated there would be 22 patients eligible for treatment in each year to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.\**

## References

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13. National Institute of Health and Care Excellence. Addison's Disease. 2016 March 2016 [cited; Available from: <https://cks.nice.org.uk/addisons-disease#!scenario>.

This assessment is based on data submitted by the applicant company up to and including 11 July 2018.

*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: [http://www.scottishmedicines.org.uk/About\\_SMC/Policy](http://www.scottishmedicines.org.uk/About_SMC/Policy)*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-

effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*