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Hydrocortisone granules in capsules for opening (Alkindi) as replacement therapy in pediatric patients with adrenal insufficiency

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ABSTRACT

Introduction: Treatment of pediatric adrenal insufficiency (AI) has been challenging due to a lack of dose and age appropriate hydrocortisone preparations for children. Hydrocortisone granules in capsules for opening (Alkindi) is the only licensed replacement therapy specifically designed for use in pediatric adrenal insufficiency.

Areas Covered: The high unmet need of the pediatric AI patient population for a licensed, dose-appropriate hydrocortisone formulation and the development and approval of hydrocortisone granules in capsules for opening for pediatric AI.

Expert opinion: To date, treatment of children with AI has relied on parents or pharmacists crushing tablets of hydrocortisone. Pediatric patients have suffered from over- and under-treatment with poor health outcomes. Hydrocortisone granules in capsules for opening provides accurate, age-appropriate dosing, allowing appropriate dose titration for the growing child. The granule-based formulation is taste masked to hide the bitterness of hydrocortisone, and in clinical trials was well tolerated and easily administered to children. The granules can be administered either directly to the mouth or sprinkled onto soft food or yogurt. Hydrocortisone granules in capsules for opening provides the first licensed treatment option specifically designed for pediatric patients with AI.

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Adrenal insufficiency; congenital adrenal hyperplasia; pediatric use marketing authorization; pediatrics; granules; sprinkle; hydrocortisone

1. Overview of the adrenal insufficiency market

Adrenal Insufficiency is caused by a failure of adrenal cortisol synthesis. It may be primary, arising from a disorder of the adrenal gland, or secondary due to disorder in another part of the hypothalamic-pituitary-adrenal axis. In young children, the commonest cause of AI is Classical Congenital Adrenal Hyperplasia (CAH) with an incidence of 1 in 10,000–20,000 live births [1–4]. Patients with adrenal insufficiency are at risk of death from an adrenal crisis unless cortisol is replaced effectively. In CAH, the pituitary gland responds to low cortisol levels by overstimulating the adrenal glands, resulting in over-production of adrenal androgens. Thus, in addition to adrenal insufficiency, patients with CAH may suffer from hyperandrogenism, virilization, early pubarche, accelerated childhood growth, early epiphyseal fusion, Testicular Adrenal Rest Tumors (TART), gonadal hypofunction and later subfertility. Hydrocortisone replacement therapy is life-saving and limits the impact of hyperandrogenism; however, treatment is impacted by inadequate glucocorticoid replacement which can result in poor health outcomes including adrenal crisis, poor growth, early puberty, obesity, hypertension, depression and increased risk of cardiovascular disease, osteoporosis and subfertility later in life [1,5–8]. Guidelines state that the native hormone, hydrocortisone (cortisol), should be used as glucocorticoid replacement therapy in children, since long-acting synthetic glucocorticoids like prednisolone and dexamethasone are more potent growth suppressors [9,10]. It is recommended that pediatric doses should be individualized to the needs of the patient, and in the range of 8–10 mg/m^2 body surface area (BSA)/day for AI and 10–15 mg/m^2/day in CAH, in 3 divided doses [9,10], with individual doses of 1–2 mg at each time point in infants, and dose titrations as low as 0.5 mg required to achieve this dosing regimen in the growing child [11] (Figure 1).

Prior to the introduction of hydrocortisone granules in capsules for opening, available oral hydrocortisone formulations in Europe were 10 or 20 mg tablets, some of which bear score marks to facilitate splitting to prepare lower doses. These formulations are unsuitable and problematic for several reasons. Firstly, even a quartered 10 mg tablet is an excessive hydrocortisone dose in young patients. Secondly, the dose accuracy of quarters prepared by splitting 10 mg tablets produces dosages outside of the range recommended in the European Pharmacopoeia more than 50% of the time [12]. Moreover, changes in manufacturing of hydrocortisone tablets optimized for adult use can lead to difficulties when parents crush tablets [13]. Thirdly, a patient survey conducted in UK showed that more than 50% of doses cannot be prepared from quartered tablets (i.e. dose is not divisible by 2.5), the same study showed that more than 25% of parents had never been trained to prepare doses [14]. Parent and caregiver concern about accuracy of doses prepared in this way causes distress, with carers describing the difficulties of manipulating medicines vital for their young children, and resultant worry, on top of the other stresses of parenthood [15]. Hydrocortisone is virtually insoluble in water and may

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Box 1. Drug summary box

Drug name Hydrocortisone granules in capsules for opening

Phase IV

Indication Replacement of adrenal insufficiency in infants, children and adolescents (from birth < 18 years old in Europe; < 17 years old in the US)

Mechanism of action Immediate-release hydrocortisone; synthetic form of naturally occurring glucocorticoid hormone cortisol. Pleotropic effects through activation of the glucocorticoid receptor in multiple tissues.

Route of administration Oral.

Pivotal trials Infacort 003 study, single arm pharmacokinetic study of drug in children aged from birth to 6 years with adrenal insufficiency and Infacort 004 a prospective study in children 0-7 years with AI treated with hydrocortisone granules. To our knowledge the first published interventional prospective studies in this age and patient group.

adhere to plastics used during preparation [16], however, attempting to dissolve hydrocortisone in water to obtain low doses for pediatric patients is common [14]. A laboratory study concluded that liquid hydrocortisone in water is a suspension rather than a solution, the volume used does not correlate with dose delivered, and in one case the delivered dose was more than 250% of the target dose [14]. Unlicensed pharmacy-prepared hydrocortisone suspensions are available in some countries but current guidelines specifically recommend against their use due to uneven hydrocortisone distribution in liquid form [10,17].

Pharmacists often prepare unlicensed low dose hydrocortisone capsules and mix with sucrose or lactose to overcome the inherent bitterness of hydrocortisone. However this can cause dental caries and is problematic in children with lactose deficiency [18]. Access to pharmacies offering this service is variable with some parents traveling distances to obtain low dose compounded product. Up to 25% of compounded batches obtained from patients across Germany did not fulfil the quality acceptance criteria of the European Pharmacopoeia when studied and so could not ensure safe therapy for patients, some batches contained no hydrocortisone and others 200% of labeled content [6]. In Sweden, severe quality issues were noted in pre-filled hydrocortisone capsules manufactured by one of the national extemporaneous medicine pharmacies with some capsules found to contain no active substance or inaccurate amounts of active substance, which resulted in the Swedish Medicines Agency's announcement to withdraw batches of ex tempore pharmacy manufactured capsules [19]. A German regional pharmacy association recommended replacing compounded products with licensed medicines during the coronavirus epidemic [20].

The aims of treatment in CAH are replacement of cortisol and control of excess androgen levels while limiting adverse outcomes associated with glucocorticoid overtreatment as described below. Inconsistent hydrocortisone dosing makes controlling CAH challenging and both under-and over-treatment can lead to severe clinical consequences (Table 1).

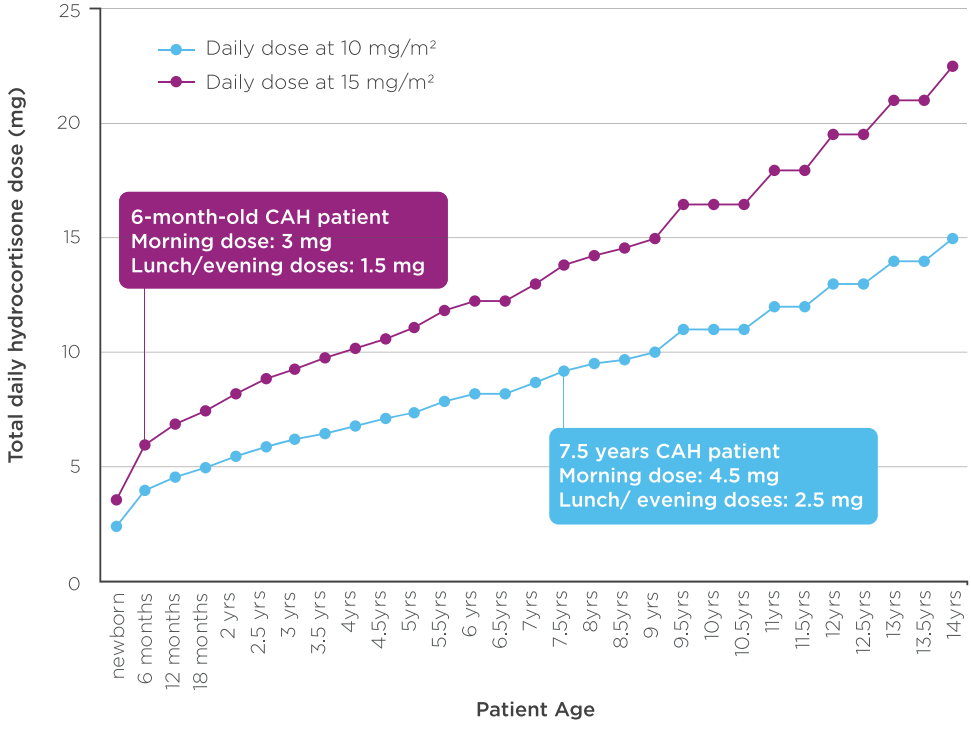

Figure 1. Increasing total daily hydrocortisone dose by age required by a child with AI or CAH treated with daily doses of either 10 mg/m^2/day (blue line) or 15 mg/m^2/day (purple line) according to the guidelines. The boxes highlight example patients at different ages and indicate the need for dose increments between 0.5 and 1 mg. Assumptions of child growth based on World Health Organization (WHO) Child Growth Standards. There is no unified guidance on the proportion of dose required at different times of day, and illustrated examples are based on common practice.

Table 1. Details of reported cases of treatment complications in patients with CAH or AI attributed to issues associated with compounded hydrocortisone.

Formulation	Outcome	Ref
Pharmacy compounded capsules	5-year-old female CAH patient, considered treatment compliant, presented with accelerated growth and elevated androgens. Her prescribed capsules showed variable filling. A new hydrocortisone batch was provided which immediately improved disease control.	[6]
Pharmacy compounded capsules	Case reports of 3 female CAH patients, aged 2 months, 6 months and 7 years who developed Cushing's syndrome due to overdosed hydrocortisone in wrongly produced capsules.	[8]
Pharmacy compounded capsules	Case report of 20-month-old female CAH patient developing Cushing's syndrome after inadvertently receiving excessive hydrocortisone in compounded form.	[7]
Pharmacy compounded tablets	Side effects reported by the Dutch national pharmacovigilance center: Adrenal crisis was reported in 4 adult CAH/AI patients, in each case occurring when switching between products produced by different pharmacies	[21]
Parent compounded tablets	Case report of 6-year-old female CAH patient developing Cushing's syndrome while taking hydrocortisone tablets crushed and dispersed in water.	[30]
US licensed hydrocortisone suspension	Center observed suboptimal hormone control levels in cohort of pediatric CAH patients after suspension formulation was changed. Patients (N = 19) were switched to hydrocortisone tablets at 90% of prior dose. Before therapy switch 19/19 had elevated androgens, after switch 14/19 showed signs of glucocorticoid excess despite lower dose. Product was subsequently withdrawn.	[17]

1.1. Impact of glucocorticoid under-replacement

Under treatment may increase risk of life-threatening adrenal crisis, the leading cause of excess mortality in CAH [22]. Based on published literature, the frequency of adrenal crisis in children with CAH ranges from 3.4 to 10.9 crises per 100 treatment years [23–25]. In children, hypoglycemia may occur with adrenal crisis and result in severe neurologic outcomes including seizures, learning difficulties, coma and death [26]. The Dutch national pharmacovigilance center recently reported adrenal crises in 4 patients occurring as they switched between different unlicensed hydrocortisone products and highlighted that bioequivalence data are not available for compounded products (Table 1). Other long-term outcomes of under treatment in CAH include growth retardation, owing to early closure of growth plates, which contributes to reduced final height reported in CAH patients [27]. Similarly, testicular adrenal rest tumors (TART), a key predictor of male infertility, has been reported in up to 28–100% of pediatric male CAH patients, and while their development is multifactorial, optimization (intensification) of glucocorticoid therapy can shrink early stage TART and prevent their progressive enlargement [10,28,29].

1.2. Impact of glucocorticoid over-replacement

Conversely, over-treatment with glucocorticoids can cause hypertension, increased fat mass, insulin resistance, reduced bone density, striae, thinning and bruising of the skin, Cushing's syndrome, growth retardation and reduced bone density [7,8,28,30]. Thus, inaccurate dosing during childhood can impact over the lifespan of the patient. Several case reports have highlighted extreme situations in which hydrocortisone dose inaccuracies led to cases of iatrogenic Cushing's syndrome (Table 1). A meta-analysis of studies in treated CAH patients reported a mean adult height score of −1.4 SD (10 cm) below the population mean [27], and a number of analyses have reported that short final height or predicted final height correlate with higher glucocorticoid doses [31–34]. Similarly, glucocorticoids are well known to increase osteoporosis and fracture risk in adults, higher glucocorticoid doses during adolescence have also been proposed have a detrimental impact on bone density in adulthood [35].

1.3. Regulation of compounded medicines

Compounding hydrocortisone results in an unlicensed product which is not regulated and quality controlled to the level of a licensed drug where Good Manufacturing Practice (GMP) regulations mean that every aspect of manufacturing must be described, controlled and regularly assessed. In a licensed product the active ingredient must be controlled within strict parameters, usually 95–105% of the label claim [36]. In contrast there is no requirement to produce compounded medicine to GMP and the process is less regulated, resulting in the Federal Drug Administration (FDA) warning that; 'FDA does not verify the safety, or effectiveness of compounded drugs' [37]. Similarly there is little regulation on the use of excipients such as colorings and sweeteners, e.g. sucrose or lactose which are added to some compounded hydrocortisone products to improve taste, but are prohibited in pediatric medicines by the European Medicines Agency (EMA) [18,38]. In Europe, the EMA has made specific commitments to the development of medicines tailored for children through the Pediatric Use Marketing Authorization (PUMA) process, namely to replace the current practice of off-label manipulation of pharmaceuticals indicated for adults, or pharmacy-compounded medications [39]. All EU-member states are expected to be committed to the policy of the EMA in opting for registered instead of unlicensed products particularly when related to reimbursement of essential therapies for vulnerable children with life-threatening conditions. Furthermore, licensed medicines are required to have a comprehensive clinical data package, pharmacovigilance surveillance, Patient Information Leaflets and Summary of Product Characteristics, Medical Information support and to comply with the EU Falsified Medicines Directive, but this is not the case with unlicensed medicines.

2. Introduction to hydrocortisone granules in capsules for opening

Hydrocortisone granules in capsules for opening (Diurnal Europe B.V., The Netherlands.) is a granule formulation utilizing multiparticulate technology. The maximum granule diameter is controlled to 0.8 mm which is significantly smaller than FDA Guidance to industry on sprinkle formulation limits of 2.5 mm diameter, allowing for swallowing of granules by neonates without causing choking [40]. Each granule has an

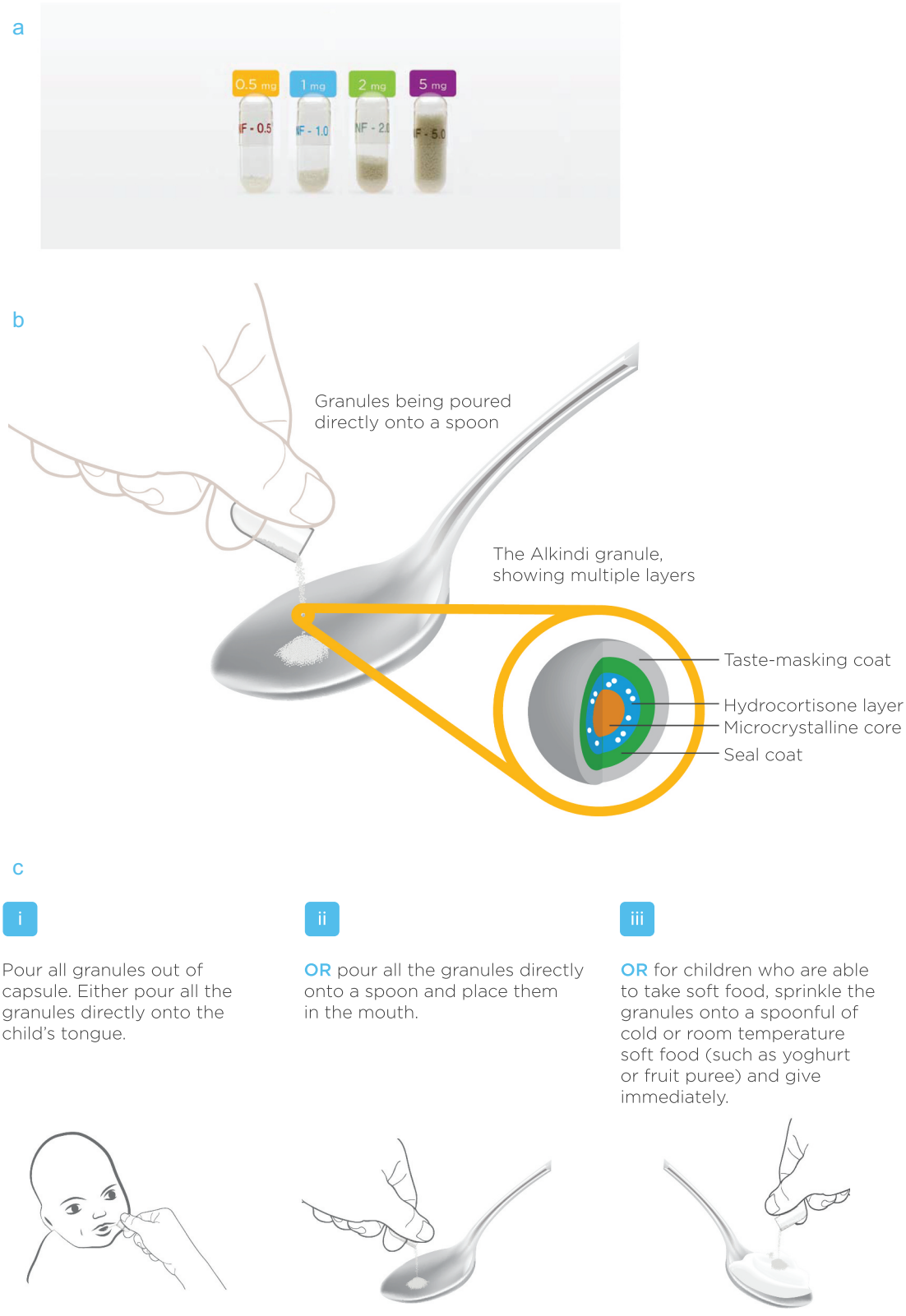

Figure 2. A: Hydrocortisone granules in capsules for opening in 0.5, 1, 2 and 5 mg doses. B: The hydrocortisone granule showing multiple layers. C: The 3 methods of administration described in full in the patient information leaflet, i, directly from the capsule; ii, using a spoon; iii, sprinkled onto a spoonful of soft food. Additional information: Once the granules are administered give a drink (e.g. water, milk) immediately to ensure the granules are swallowed. The capsule is a carrier only and should not be swallowed. If granules are given with soft food, administer them immediately (within 5 minutes) and do not store for future use. Never add granules to liquid before administration as this can result in less than the full dose being given, and might also dissolve the taste masking of the granules allowing the bitter taste of hydrocortisone to become apparent.

Table 2. Pharmacokinetic parameters derived from European and US bioequivalence studies shown in Figure 3A and 3B. The ratio (CI) of hydrocortisone granules in capsules for opening and reference product indicated bioequivalence in each case in fasted subjects, additionally the Cortef study showed bioequivalence in subjects administered Alkindi or Cortef in the fed state. As expected, delayed T_{max} was seen in the fed state.

	Cmax (nmol/L)	AUC0-inf (h*nmol/L)	Tmax (h)
European reference product; Auden Mckenzie hydrocortisone. Fasted subjects			
Hydrocortisone granules 10 mg	566	1602	
Hydrocortisone 10 mg	598	1586	1.00
Hydrocortisone granules/Reference ratio (90% CI)	95 (84–107))	101 (96–107)	
US reference product; Cortef, Pfizer. Fasted subjects			
Hydrocortisone granules 20 mg	1310	4090	0.75
Hydrocortisone 20 mg	1190	4340	1.00
Hydrocortisone granules/Reference ratio (90% CI)	110 (102–118)	94 (88–101)	
US reference product; Cortef, Pfizer. Fed subjects			
Hydrocortisone granules 20 mg	727	3620	1.25
Hydrocortisone 20 mg	803	3490	1.50
Hydrocortisone granules/Reference ratio (90% CI)	91 (83–99)	105 (100–110)	

inert cellulose core, sprayed with hydrocortisone, which is sealed and coated with a taste-masking layer which has been shown to mask the bitter taste of hydrocortisone (Figure 2) [41]. The granules are contained within a size 00el transparent capsule that is not intended to be swallowed by the patient but instead is opened for dosing (Figure 2). Hydrocortisone granules in capsules for opening is available in 4 dose strengths; 0.5, 1, 2, and 5 mg, by combining the available capsules all possible pediatric hydrocortisone doses can be provided accurately to address the needs of individual patients (Figure 1). The granules are minute; for example, the 0.5 mg capsule contains ~900 granules.

2.1. Cortisol biology

Hydrocortisone has been used in humans for more than 60 years and is identical to the innate hormone cortisol. Like other steroids, cortisol binds to an intracellular receptor which, after migrating to the nucleus of the cell, upregulates or downregulates gene expression. Hydrocortisone also acts through non-genomic mechanisms [42]. Hydrocortisone is rapidly and virtually completely absorbed from the fasted alimentary system (bioavailability is ~100%) with Tmax reached about 60 minutes [43]. Cortisol is highly protein bound mostly by cortisol binding globulin, with a smaller amount of albumin binding. This leads to non-linear pharmacokinetics as higher doses of hydrocortisone are more rapidly cleared due to saturation of the protein binding [43,44]. Metabolism of cortisol is by renal 11β-Hydroxysteroid dehydrogenase type 2 (11β-HSD2) to inactive cortisone whilst hepatic and adipose 11β-HSD1 converts cortisone to cortisol. Cortisol, cortisone and downstream metabolites allo-tetrahydrocortisol, tetrahydrocortisol and tetrahydrocortisone, are all renally excreted [45].

Our understanding of the safety of steroids stems from their use in high dose as anti-inflammatories. Adverse events are in many cases dose dependant, and so many adverse events are less relevant to low dose adrenal replacement where the aim is to reproduce the natural physiology. Drug interactions are seen in patients with adrenal insufficiency: CYP3A4 induction by e.g. rifampicin or phenytoin increases the clearance of steroids requiring a hydrocortisone dose increase, whereas CYP3A4 inhibition by e.g. Antiretrovirals, antifungals or grapefruit juice will increase cortisol concentrations necessitating hydrocortisone dose reduction [46–48].

2.2. Clinical study data

Hydrocortisone granules in capsules for opening was subject to an EU Pediatric Investigation Plan (EMEA-001283-PIP-0-12) leading to a Pediatric Use Marketing Authorization (PUMA). In the US the development of hydrocortisone granules in capsules for opening (marketed as Alkindi Sprinkle) was under an Investigational New Drug (IND) dossier leading to a 505(b)(2) pathway approval. The development program included bioequivalence studies using reference products in the EU (Auden Mckenzie Hydrocortisone, 10 mg) and US (Cortef, Pfizer, 20 mg) at phase 1, before a phase 3 study to demonstrate appropriate exposure in pediatric adrenal insufficiency patients. To allow measurement of hydrocortisone in the bioequivalence studies healthy adult volunteers were treated with dexamethasone to suppress their endogenous cortisol production. The studies compared the pharmacokinetics of hydrocortisone granules in capsules for opening with the reference hydrocortisone tablets, examined dose proportionality at doses of 0.5, 2, 5, and 10 mg and the impact of the fed and fasted state on the product's pharmacokinetics. The studies showed that hydrocortisone granules in capsules for opening were bioequivalent to immediate release hydrocortisone in the fasted and fed state (Table 2 & Figure 3)[41].

The ability to mix medicine with food provides flexibility and ease of administration when using medicines in children, particularly in infants or children unwilling to swallow tablets [49–51]. Sprinkling medication onto food can alter its pharmacokinetic characteristics. To demonstrate hydrocortisone granules in capsules for opening compatibility with child appropriate fluids and soft foods; in vitro and in vivo studies were conducted [52–54]. In vitro data and modeling confirmed that pediatric patient exposure to hydrocortisone from the granules is unlikely to be impacted by co-administration with water, breast, cow or formula milk, orange, apple or tomato juice, or soft foods such as apple sauce or yogurt. This was followed by an in vivo study, again in healthy adult volunteers, after dexamethasone suppression, which demonstrated that hydrocortisone granules sprinkled onto soft food or yogurt are bioequivalent to those administered directly to the back of the tongue (Figure 3c) [54]. These studies informed instruction in

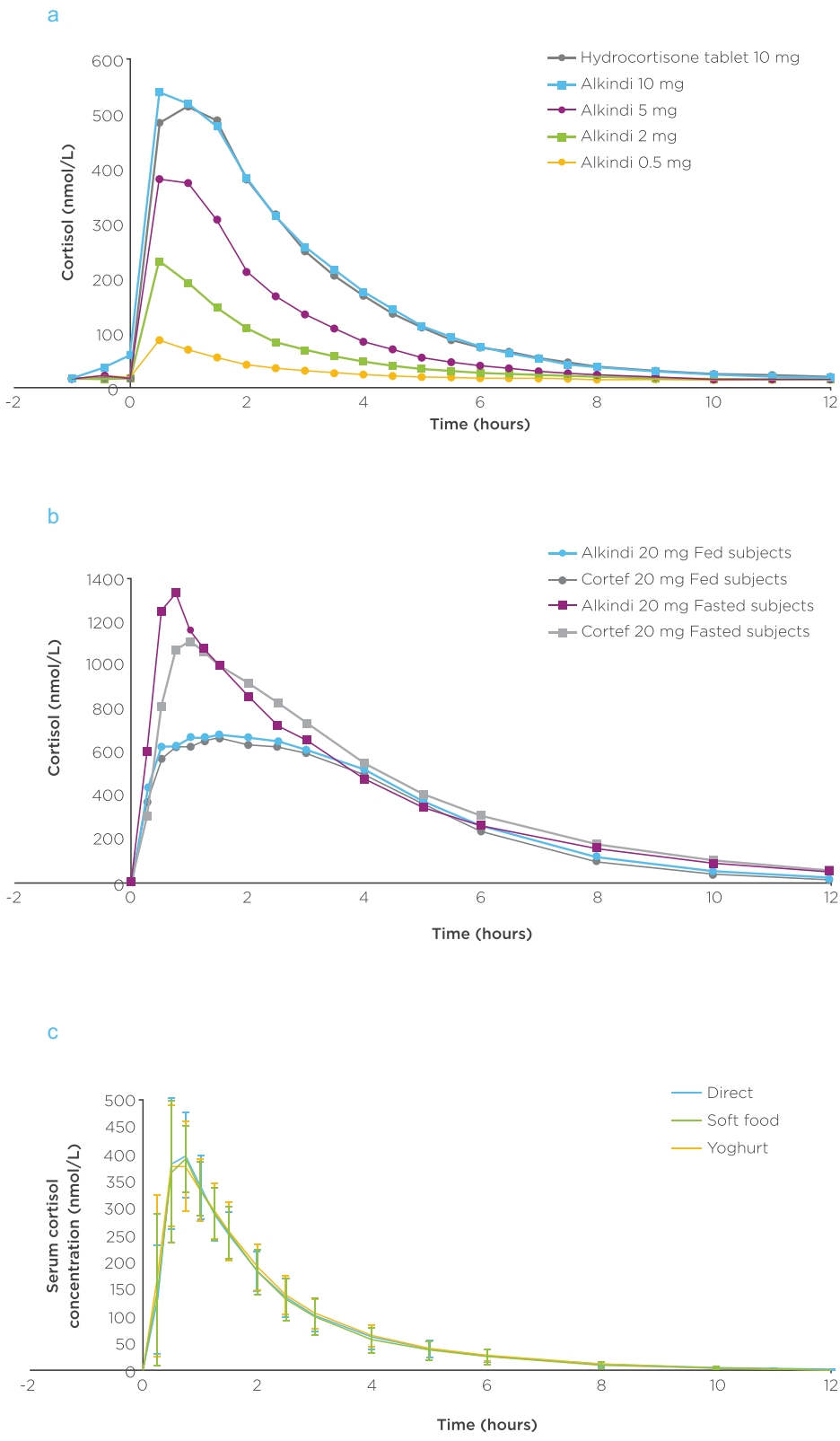

Figure 3. Bioequivalence studies. A: Mean serum cortisol concentrations in dexamethasone suppressed healthy adults (n = 16) after administration of either 10 mg oral hydrocortisone tablet (European reference product; Auden Mckenzie) [gray line]or hydrocortisone granules in capsules for opening 10, 5, 2 or 0.5 mg [blue, purple, green and orange lines respectively]. Derived pharmacokinetic parameters shown in Table 2. B: Mean baseline-adjusted serum cortisol concentrations in fed and fasted dexamethasone suppressed healthy adults (n = 24) after administration of 20 mg oral hydrocortisone tablet (USA reference product; Cortef, Pfizer) or hydrocortisone granules 20 mg. Purple squares: Hydrocortisone granules (fasted state); gray squares: Cortef (fasted state); blue circles: Hydrocortisone granules fed state; gray circles: Cortef fed state. Derived pharmacokinetic parameter shown in Table 2. C: This graph is adapted from [54] and is licensed under Creative Commons CC BY-NC-ND. Mean baseline-adjusted cortisol concentrations in dexamethasone suppressed healthy adult volunteers (n = 18) after administration of 5 mg hydrocortisone granules either directly to the back of the tongue (blue line), sprinkled onto 5 mL soft food (apple sauce [green line]) or sprinkled onto 5 mL yogurt (orange line).

the patient information leaflet and SmPC (Figure 2), advising administration of hydrocortisone granules either directly or sprinkled onto soft food or yogurt. Administration should always be followed by a drink, in order to ensure granules are swallowed, however, the granules should never be added to liquid since the taste-masking layer will dissolve and the full dose may not be administered.

The phase 3 study (EudraCT number 2014–002265-30) was performed at the Charité hospital in Berlin [55] and is the first prospective study of hydrocortisone for treatment of AI in this age group. This was an open-label single dose study conducted in patients with pediatric AI (n = 24), run in sequential age cohorts to maximize safety (Cohort 1: n = 12 patients aged 2- >6 years; cohort 2: n = 6 patients aged 28 days – 2 years; cohort 3: n = 6 patients aged less than 28 days). All patients received hydrocortisone granules in capsules for opening in the morning at the same dose as their current immediate release hydrocortisone. Dosing was at least 8 hours after the patients' previous dose of hydrocortisone. The dose was at least 2 hours after food in children aged 12 months or more, and 45 minutes after food in those aged less than 12 months. Blood samples were taken at 0, 60 and 240 minutes after dosing and the primary endpoint was maximum serum cortisol concentration up to 240 minutes after administration. Secondary endpoints included palatability (for which new questionnaires were developed for parents and patients), adverse events and vital signs recorded during the study. Of the 24 children studied, 23 had CAH and one patient was hypopituitary, the median age was 3.25 years, the youngest being 16 days old, 46.8% were female and all subjects were Caucasian. All children were successfully dosed, the median dose being 2 mg. Peak cortisol levels were seen at 60 minutes in all subjects (Figure 4). Cortisol absorption and clearance was similar to findings in previous studies of children dosed with immediate release hydrocortisone [56]. The hydrocortisone C_{max} was similar to that seen at peak concentrations of cortisol in unaffected children with normal physiology [57]. The

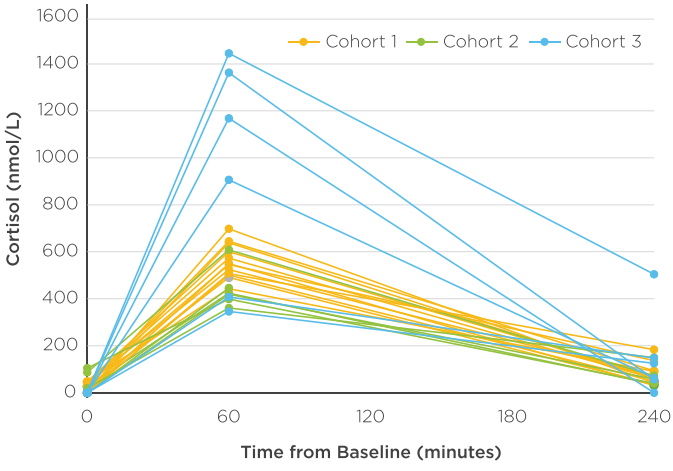

Figure 4. Cortisol levels in individual pediatric AI patients in the phase 3 study measured at baseline and 60 and 240 min after administration. Cohort 1 (orange lines): patients aged 2 to <6 years, n = 12; Cohort 2 (green lines): patients aged 28 days to 2 years, n = 6; and Cohort 3 (blue lines): patients aged from 1 to 28 days, n = 6. Higher cortisol levels in cohort 3 reflect higher doses per body surface area used in this cohort consistent with guidelines.

hydrocortisone granules in capsules for opening was generally well received by parents and children alike. In total, 82.6% of parents agreed/strongly agreed that their child found swallowing the granules easy and 95.5% said that they would prefer it for their child's treatment over their usual hydrocortisone formulation. Six of the 12 children in the oldest cohort were administered an age appropriate questionnaire, for all questions the majority of children had a positive or neutral response; 83% showing positive or neutral response to the smell of the granules, 66.7% showing positive or neutral response to swallowing the granules, 100% showing positive or neutral response to the taste of the granules, 66.7% positive or neutral response to how the granules feel in the mouth, and 83.7% a positive or neutral response when asked if they would take the medicine again. There were no serious adverse events reported in the study, all reported adverse events were mild or moderate (the most common reported were diarrhea, vomiting and rash) and not considered attributable to investigational product [55].

After completing the phase 3 study subjects could choose to participate in a long-term extension study with the objective of studying the safety and tolerability of hydrocortisone granules in capsules for opening [58]. Seventeen children with CAH (9 male) and 1 with hypopituitarism (male) aged from birth to 6 years, had their hydrocortisone medication changed from pharmacy compounded capsules to hydrocortisone granules in capsules for opening and were followed prospectively for over 2 years. In CAH patients, therapy was adjusted by 3-monthly 17-hydroxyprogesterone (17-OHP) measurements. The following parameters were recorded: hydrocortisone dose, height, weight, pubertal status, adverse events, and incidence of adrenal crisis. Study medication was given 3 times daily, and median duration of treatment (range) was 795 (1–872) days with 150 follow-up visits. Hydrocortisone doses were altered on 40/150 visits, 32 according to salivary measurements and 8 on serum 17-OHP levels. Median daily hydrocortisone dose mg/m^2 (range) at study entry in 3 different age groups; 2–8 years, 1 month –2 years, and <28 days, was 11.9 (7.2–15.5), 9.9 (8.6–12.2) and 12.0 (11.1–29.5) and at end of study was 10.2 (7.0–14.4), 9.8 (8.9–13.1) and 8.6 (8.2–13.7) respectively. Disease control remained good, as shown by lack of pubertal development and no trends for accelerated or reduced growth. Over the course of the study, 2/3 of the children converged toward their expected height centile, the mean difference between z-scores of actual height and target height (SD) decreased from 1.04 (0.71) to 0.89 (0.72). Z-scores for weight decreased toward the 50th centile in 50% of the patients. During the study period of more than 2 years, 193 adverse events were recorded, mainly common childhood illnesses, however none of these were considered related to hydrocortisone granules in capsules for opening and there were no adrenal crises. This is the first prospective long term study of any glucocorticoid treatment in children with AI or CAH and shows that accurate dosing and monitoring enables hydrocortisone doses at the lower end of the

recommended dose range, and normal growth, without occurrence of adrenal crises [58].

2.3. Real world experience of hydrocortisone granules in capsules for opening

Since the first patient was treated with Alkindi in 2015, through to today, an estimated 550 patients have been treated commercially. While this manuscript was in preparation a report of an adrenal crisis occurring in an infant treated with hydrocortisone granules in capsules for opening was received. The crisis occurred around 48 hours after that patient switched from soluble hydrocortisone tablets to hydrocortisone granules. There were no signs of acute illness, nor any indication that the granules had been administered incorrectly nor evidence of malabsorption. Review conducted in liaison with Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA noted that owing to the insolubility of hydrocortisone, preparation of hydrocortisone soluble tablets not in accordance with the manufacturer's instructions may risk variable dosing and make conversion to other forms of hydrocortisone in younger children difficult. Similarly, variable dosing may result from the use of crushed or compounded hydrocortisone formulations in the youngest children. Detailed guidance was made available in a Direct Healthcare Professional Communication (DHPC) and the product information updated to highlight the importance of patient monitoring in the week after switch from compounded hydrocortisone [59].

2.4. Administration via nasogastric tubes

Hydrocortisone administration via nasogastric (NG) tube is required in sick children with adrenal insufficiency, in some cases of sepsis and occasionally in premature infants; however, use of hydrocortisone granules directly down the NG tube is contraindicated due to risk of blocking fine bore NG tubes. This finding came from an in vitro study to measure hydrocortisone recovery after passing through NG tubes for three formulations; suspension, crushed tablets in water, and hydrocortisone granules in capsules for opening [16]. Even before passage through the NG tube, hydrocortisone recovery was low for all formulations examined; between 30%-78%, presumably due to hydrocortisone sticking to the syringes. Adding a 'flush' of the administration syringe improved recovery. Hydrocortisone recovery after passage with flushing through 6-12Fr gauge NG tubes was variable: liquid suspension 61–92%, crushed tablets 40–174%, hydrocortisone granules 61%-92%. Importantly, hydrocortisone granules occluded 6 and 8Fr NG tubes; however, mixing hydrocortisone granules with water and using a filter needle to avoid granules entering the NG tube gave a recovery of 74–98% of the intended dose, similar to other preparations.

2.5. Current status of hydrocortisone granules in capsules for opening

Hydrocortisone granules in capsules for opening was authorized in the 28 countries then in the European Union in February 2018 for replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old) Box 1. Since then, it has been widely commercialized across Europe including in Germany, Italy and the UK with an estimated 550+ pediatric AI patients treated, the youngest of whom commenced hydrocortisone granules in capsules for opening at 4 days old (personal communication). The same hydrocortisone granule formulation, known in the USA as hydrocortisone oral granules was approved by FDA in September 2020, as replacement therapy for Adrenocortical Insufficiency (AI) in children under 17 years of age, with the brand name for Alkindi Sprinkle. In Australia, hydrocortisone granules in capsules for opening was granted Orphan Drug Designation and approval by the Australia Therapeutic Goods Administration (TGA) as a replacement therapy for adrenal insufficiency (with no specific age range). In Israel, hydrocortisone granules in capsules for opening has received approval from the Ministry of Health as a replacement therapy of adrenal insufficiency (AI) in infants, children and adolescents (from birth to <18 years old).

3. Conclusions

Hydrocortisone granules in capsules for opening is the first formulation of immediate release hydrocortisone designed and licensed for use in pediatric adrenal insufficiency with doses of 0.5, 1, 2 and 5 mg. It provides a licensed treatment option for consistent and accurate dosing in children with adrenal insufficiency and is currently commercialized across Europe and the USA.

4. Expert opinion

Adrenal insufficiency is a rare disease characterized by an inability to secrete cortisol and Congenital Adrenal Hyperplasia (CAH) is the commonest cause in the pediatric population. Adrenal insufficiency results in death through an adrenal crisis unless cortisol is replaced; hence, life-long glucocorticoid replacement therapy is required. Prior to the approval of hydrocortisone granules in capsules for opening, treatment of pediatric patients has been difficult due to a dearth of licensed appropriate glucocorticoid preparations for children. Pediatric patients need child-appropriate formulations, in doses as low as 0.5 mg which can be tailored to clinical needs as they grow. Previously oral tablets in doses designed for adults were the only approved formulations, therefore pediatric patients relied on pharmacy- or parent- compounded hydrocortisone preparations (e.g. hydrocortisone powder, 'special' solution, or crushed tablets). As compounded products are not licensed, they are not subject to the level of regulation and quality control under Good Manufacturing Practice (GMP) regulations that apply to a licensed drug. Hence, compounding hydrocortisone has multiple issues including inconsistent and inaccurate dosing with increased risk of under- and over- treatment associated with potential adverse outcomes, such as adrenal crisis, poor disease control impacting both short- and long- term outcomes, and practical and sometimes distressing problems for parents and carer givers. Hydrocortisone granules in capsules for opening was awarded a pediatric use marketing authorization (PUMA) by the EMA in

2018 for replacement therapy for AI in children up to 18 years. More recently the product was also approved by the FDA as replacement therapy for AI in children up to 17 years and Australian TGA, without age restriction. Hydrocortisone granules in capsules for opening is the first approved hydrocortisone formulation for the treatment of AI specifically designed for use in children. Its approval was supported by the first interventional phase 3 study of any oral hydrocortisone product in neonates, infants and children. Hydrocortisone granules in capsules for opening is available in 0.5, 1, 2, and 5 mg strengths, allowing accurate dosing and flexibility to tailor dosing based on patients' needs. The granules are contained within a transparent capsule that is opened for dosing and are then administered directly or mixed with food. Each granule has an inert cellulose core, coated with hydrocortisone and covered by a taste masking layer to obscure the bitter taste of hydrocortisone being experienced by the patient, potentially increasing compliance. The formulation is bioequivalent to current immediate-release hydrocortisone products. Clinical studies in neonates and young children with adrenal insufficiency showed cortisol levels after dosing similar to those seen in healthy children. This novel formulation of hydrocortisone was well tolerated without occurrence of adrenal crisis in clinical trials and favored over current therapy by parents and children. Hydrocortisone granules in capsules for opening provides the first licensed treatment option specifically designed for accurate dosing in children with adrenal insufficiency.

Declaration of interest

R Ross is the director of Diurnal LTD and all other authors are employees of Diurnal LTD. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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