

## Alkindi® Hydrocortisone 0.5mg, 1mg, 2mg and 5mg granules in capsules for opening

Alkindi® has recently been launched as a licenced hydrocortisone for replacement therapy of adrenal insufficiency in children and adolescents (from birth to <18 years old).<sup>1</sup> The dose must be individualised according to response in the individual patient and the lowest possible dosage should be used. 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.<sup>1</sup>

The capsule should not be taken, it needs to be opened and the granules poured directly onto the child's tongue or sprinkled onto a spoonful of cold room temperature soft food immediately before being taken. Granules cannot be administered via a nasogastric tube as there is a risk of blockage.<sup>1</sup>

A potential risk of choking on the capsule has been identified in the European Public Assessment Report (EPAR) report for Alkindi®, however there have been no incidents of this occurring and no data is available to suggest this happens currently with compound hydrocortisone that is traditionally dispensed in capsules.<sup>2</sup>

Another important risk identified in the EPAR report is the accidental aspiration of granules; however there was no evidence of this occurring in the clinical trials and the product is contra-indicated in dysphagia or in premature neonates where oral feeds are not tolerated.<sup>2</sup>

### What is the problem?

Hydrocortisone doses must be individualised to patients which creates an issue for small doses needed in children.<sup>3</sup> Only immediate release formulations are recommended for use in children for the treatment of adrenal insufficiency.<sup>3</sup> The following solutions have been used, but are not ideal:

- **Using muco-adhesive hydrocortisone 2.5mg tablets for some of the smaller doses.**

In December 2018, the MHRA issued an alert on Hydrocortisone muco-adhesive buccal tablets stating that these should not be used off-label for adrenal insufficiency in children due to serious risks of insufficient cortisol absorption and life-threatening adrenal crisis.<sup>4</sup>

- **Splitting 10mg tablets.**

Tablets are scored and can therefore be halved or quartered; however splitting tablets can result in unequal parts resulting in unequal doses. This can also cause a loss of critical mass of the tablet due to crumbling.<sup>5</sup>

- **Crushing and dispersing 10mg tablets**

Crushing and dispersing 10mg tablets in water and measuring a dose for smaller doses can result in unacceptably high variability in dosing.<sup>5</sup>

- **Prescribing of unlicensed specials**

There are general concerns relating to the bioavailability of liquid specials and prices can vary.

- **Hydrocortisone 10mg soluble tablets**

Hydrocortisone 10mg soluble tablets are licensed for use in children, and may be an option for patients for whom a solid dosage form may be unsuitable, but are only available in 10mg tablets and therefore also not suitable to administer lower doses.<sup>5</sup> Measuring out smaller doses after the tablets have dissolved can result in unacceptably high variability in dosing.<sup>5</sup>

Alkindi® is the only licenced product currently available that can be used to give accurate dosing in children.<sup>1</sup>

### Costs <sup>3,7</sup>

Product	Quantity	NHS price
Hydrocortisone 20mg tablets	30	£6.72
Hydrocortisone 2.5mg muco-adhesive buccal tablets sugar free <b>(not licenced for adrenal insufficiency)</b>	20	£8.70
Hydrocortisone 10mg tablets	30	£18.82
Hydrocortisone 10mg soluble tablets	30	£37.50
Hydrocortisone 500 microgram granules in capsules for opening (Alkindi®)	50	£33.75
Hydrocortisone 1mg granules in capsules for opening (Alkindi®)	50	£67.50
Hydrocortisone 2mg granules in capsules for opening (Alkindi®)	50	£135.00
Hydrocortisone 5mg granules in capsules for opening (Alkindi®)	50	£337.50
Hydrocortisone 10mg/5ml oral suspension (special listed in Drug Tariff)	100ml	£43.14
Hydrocortisone 5mg/5ml oral suspension (special listed in Drug Tariff)	100ml	£35.04

### Dosing examples to show cost pressure

Recommended replacement doses of hydrocortisone are 8 to 10mg/m<sup>2</sup>/day for patients with adrenal insufficiency alone the larger dose to be given in the morning and the smaller in the evening, higher doses may be needed.<sup>3</sup>

For congenital adrenal hyperplasia (CAH) the dose is 9 to 15mg/m<sup>2</sup>/day typically in three divided doses, adjusted according to response.<sup>3</sup>

**A 5 kg baby would have a body surface area of 0.30m<sup>2</sup>.<sup>3</sup> Using a dose of 10mg/m<sup>2</sup>/day, their total daily dose would be 3mg which could be split into 2mg taken in the morning and 0.5mg in the afternoon and evening.**

- The 28 day cost for Alkindi® (using 2mg and 0.5mg capsules) would be £113.40

- The 28 day cost using the liquid special listed in the Drug Tariff (5mg/5ml strength) would be £29.46  
This is a 79% cost pressure for Alkindi®. The issues to consider would be using a licenced medicine vs an unlicensed special.
- It would not be appropriate to try and get 0.5mg doses from crushed and dispersed tablets.

**A 29 kilogram child (average age between 7-10 years old) would have a body surface area of 1m<sup>2</sup>.<sup>3</sup> Using a dose of 10mg/m<sup>2</sup>/day, their total daily dose would be 10mg which could be split into 5mg taken in the morning and 2.5mg in the afternoon and evening.**

- The 28 day cost for (using 5mg, 2mg and 0.5mg capsules) would be £378
- The 28 day cost using the liquid special listed in the Drug Tariff (5mg/5ml strength) would be £98.11  
This is a 73% cost pressure for Alkindi®. The issues to consider would be using a licenced medicine vs an unlicensed special.
- The 28 day cost of using 10mg tablets split into half and quarters would be £17.57 if one tablet were used per day or £52.69 if this was done using 3 tablets per day.  
This is an 86 to 96% cost pressure for Alkindi®. The issues to consider are the unacceptably high variability in dosing for the smaller doses.
- A combination of Alkindi® and splitting a 10mg tablet could be used (half a 10mg tablet in the morning and 2mg plus 0.5mg capsules of Alkindi® in the afternoon and evening). This could cost £206.57  
This is a 45% cost pressure for Alkindi®. The issues to consider is whether it would be suitable for patients and families who would need to use two different products to make up the dose.

#### **Older children on higher doses.**

**An older child on a dose of 20mg total daily dose could have their dose split into 10mg taken in the morning and 5mg in the afternoon and evening.**

- The 28 day cost for Alkindi® (using 5mg capsules) would be £756
- The 28 day cost using the liquid special listed in the Drug Tariff (10mg/5ml strength) would be £120.79  
This is an 84% cost pressure for Alkindi®. The issues to consider would be using a licenced medicine vs an unlicensed special.
- The 28 day cost of using 10mg tablets split into half for the 5mg doses would be £35.13 if two tablets were used per day or £52.69 if this was done using 3 tablets per day.  
This is a 99% cost pressure for Alkindi®.

For older children on higher doses, it would be more appropriate to use the tablets.

For younger children where doses needed do not fit exactly with the strengths of Alkindi® available, a liquid special may be more appropriate to prescribe.

## National Guidance

The SMC have accepted use of Alkindi® for restricted use in children under 6 for whom hydrocortisone must otherwise be individually prepared by manipulation such as by compounding (or crushing) or by the production of liquid specials. This advice is contingent on a Patient Access Scheme price available in Scotland.<sup>8</sup> There is currently no PAS price available in England in secondary care. PAS prices are not available in primary care.

There is significant cost pressure to primary care. CCGs should liaise with their secondary care colleagues to ensure patients are reviewed to ensure they are receiving the most appropriate product. Prescribing responsibility should be agreed locally.

## References

1. Summary of Product Characteristics. Alkindi® 1mg granules in capsules for opening. Diurnal Limited. Last updated 13 Feb 2019. Accessed 02/09/19 <https://www.medicines.org.uk/emc/product/9033/smpc>
2. European Medicines Agency. European Public Assessment report (EPAR) Alkindi®. Risk – management plan summary.01/03/18 Accessed 02/09/19 <https://www.ema.europa.eu/en/medicines/human/EPAR/Alkindi®>
3. Joint Formulary Committee. British National Formulary for children (online) London: BMJ Group and Pharmaceutical Press. Accessed 02/09/2019 available at <https://bnfc.nice.org.uk/medicinal-forms/hydrocortisone.html>
4. Medicines and healthcare products regulatory Agency. Drug Safety Update. Hydrocortisone muco-adhesive buccal tablets: should not be used off-label for adrenal insufficiency in children due to serious risks. 18 December 2018. Available at <https://www.gov.uk/drug-safety-update/hydrocortisone-muco-adhesive-buccal-tablets-should-not-be-used-off-label-for-adrenal-insufficiency-in-children-due-to-serious-risks>
5. Madathilethu J, Roberts M, Peak M, et al. Content uniformity of quartered hydrocortisone tablets in comparison with mini tablets for paediatric dosing. BMJ Paediatrics Open. 29 January 2018
6. Summary of Product Characteristics. Hydrocortisone 10mg soluble tablets. Colonis Pharma Ltd. Last updated 21 Jan 2019. Accessed 02/09/19 <https://www.medicines.org.uk/emc/product/9833/smpc>
7. NHS BSA Prescription Pricing Division. NHS Electronic Drug Tariff. September 2019. Accessed 02/09/19 via <http://www.drugtariff.nhsbsa.nhs.uk/#/00726198-DD/DD00725753/Part%20VllIA%20products%20H>
8. Scottish Medicines Consortium. Hydrocortisone 0.5mg, 1mg, 2mg and 5mg granules in capsules for opening (Alkindi®). 7 September 2018. Available at <https://www.scottishmedicines.org.uk/media/3758/hydrocortisone-granules-Alkindi®-final-september-2018-for-website.pdf>