IN USE PRODUCT SAFETY ASSESSMENT REPORT FOR ALKINDI® (HYDROCORTISONE) GRANULES IN CAPSULES FOR OPENING

SUMMARY OF ASSESSMENT AND ITS FINDINGS

BACKGROUND

Alkindi® (hydrocortisone) granules in capsules for opening (Diurnal Limited) was launched in the UK on 3rd September 2018. This is the first hydrocortisone product licensed solely for paediatric use for replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old). The capsules are opened and the granules are either poured directly onto the child's tongue, or the granules are poured onto a spoon and placed in the child's mouth. Alkindi® is available in strengths 0.5mg, 1mg, 2mg and 5mg. and is therapeutically equivalent to conventional hydrocortisone tablets (1, 2).

Current options for hydrocortisone use in children include: dividing or crushing immediate-release tablets, use of soluble tablets or specifically formulated specials solutions. Off-label use of hydrocortisone muco-adhesive buccal tablets has been used as an alternative, but following an MHRA alert, it should not be used by patients with endocrine disorders (3).

This review summarises practical in-use safety considerations associated with the introduction of Alkindi®. The addition of this new product to the UK market with its unusual presentation 'granules in capsules for opening' raises some safety concerns.

DETAILS OF PRODUCT (S) ASSESSED

The products assessed using the validated UKMi product assessment tool (4) were:

- Alkindi® (hydrocortisone) granules in capsules for opening 0.5mg, 1mg, 2mg and 5mg by Diurnal Limited.

Assessments were carried out with reference to: product packaging artwork and images, summaries of product characteristics (SmPC) (2), patient information leaflet (5) and European Medicines Agency (EMA) assessment report (6).

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL

Potential risks are identified below; mitigating and other necessary actions are considered in the next section.

A risk assessment of Alkindi® identified the following safety issues:

- 'Granules in capsules for opening' is a novel presentation in the UK market. A lack of familiarity with this presentation type may lead to confusion on the correct way of prescribing, dispensing, labelling and administering Alkindi®. See appendix A pictorial on administration instructions.
- The product presents a choking risk to children if the outer hard capsule is not discarded appropriately after opening and administering the granules.
- There is an inherent risk with the use of hydrocortisone in paediatrics due to complexities of calculating the dose using body surface area.
- There are a variety of hydrocortisone preparations available (buccal tablets, soluble tablets, immediate release tablets) and therefore there is potential for error through incorrect product selection at the point of prescribing (e.g. electronic prescribing systems), dispensing/supply and administration.
- Mis-selection of the wrong hydrocortisone product or the wrong strength within the Alkindi® range could result in an inappropriate amount of hydrocortisone being taken.

Healthcare organisations should consider the following as part of local formulary applications:

Recommended hydrocortisone replacement doses for adrenal sufficiency in children are complex (8-10 mg/m^2/day or 10-15 mg/m^2/day in three or four divided doses). Alkindi® is available in a variety of strengths to facilitate the administration of the majority of doses necessary for the various age groups. This is especially apparent in comparison to hydrocortisone tablets which would require splitting the tablet (off-label use) in order to provide the necessary calculated dose. Overall, Alkindi® provides the advantage of allowing greater flexibility and accuracy in administering the appropriate hydrocortisone dose to paediatric patients in a licensed way. The granules are also taste masked so the bitter taste of hydrocortisone does not cause difficulties with dosing/administration.

Administration of Alkindi® granules in capsules for opening:

- The product is not ready for administration and manipulation is required which includes four simple steps (see appendix A). This, however, increases the chance of errors occurring, particularly as the method is not commonly used in paediatrics.
- As mentioned previously the outer hard capsule should be discarded, however if this is not done appropriately after use, the capsule is a choking hazard in the age group for which Alkindi® is licensed.
- Similarly, if the capsule is inadvertently swallowed whole by young children, there is a risk of choking. Reassuringly, the capsule is commonly used for pharmaceutical products so is non-toxic and will dissolve and release its contents in the stomach; this may slightly delay the time to maximum cortisol concentration (CMax) with Alkindi, but is unlikely to be clinically significant.

Product packaging and literature:

Overall the packaging of Alkindi® was considered appropriate (see product images at the end of the report). Measures have also been taken to reduce the risk of mis-selection of the wrong product, including using different colours for the packaging of the different strengths. Suitable professional and patient information is also available in the form of a SmPC and a well-illustrated patient information leaflet (PIL). Some of the areas where caution may need to be taken include:

- There is no designated area for a dispensing label on the inner bottle and therefore there is a risk of important information: 'Do not swallow the capsule, risk of choking', being covered during the dispensing/labelling process.
- Action to be taken in the circumstances of the capsules being inadvertently swallowed whole or in part. Currently, the SmPC or PIL does not address this situation.
- All strengths of Alkindi® are presented as clear capsules with small text to differentiate between strengths. This could be potentially confusing for patients or carers as multiple strengths may be necessary to administer the correct dose.
- There is no designated line to handwrite the open date on the bottle. This could cause an issue if the outer box is discarded.

POTENTIAL NEXT STEPS AND MITIGATION ACTIONS

To support safe use of Alkindi® all providers and commissioners of NHS healthcare should consider:

- Carrying out local risk assessments as part of any formulary applications for Alkindi®. This risk assessment should inform any purchasing and procurement decisions made by Trusts to stock the product.
- Ensuring Alkindi® is prescribed using both brand and generic name, and product type: granules in capsules for opening.
- Reviewing and amending prescribing/dispensing systems to ensure risk of selecting another similar product is minimised (such as having a designated line for the variety of oral hydrocortisone preparations e.g. granules in capsules for opening; soluble tablets; muco-adhesive buccal tablets available in the organisation).
- Raising awareness (pharmacy, nursing staff and prescribers) of the availability of Alkindi® and

the potential for errors by selecting the wrong product.

- Standardised directions on dispensing labels e.g. Hydrocortisone 2mg granules in capsules for opening. Give the contents of ONE capsule THREE times a day by opening the capsule and administering all of the granules inside. Immediately discard the empty capsule after use.
- The best method to label the product, being mindful not to occlude important information on the inner bottle (e.g. labelling both the box and the bottle; 'flagging' the label on the inner bottle)
- Appropriate counselling of patients/carers on administration of the product and ensuring they are aware of the importance of disposing the outer shell.
- Liaising with suppliers of electronic prescribing systems on how to minimise the risk of selecting the wrong product within their systems.

In addition to actions for the NHS, this review also highlighted points for Diurnal Limited, the manufacturer of Alkindi® to consider:

- Adding information to the SmPC and PIL on action to be taken in the circumstances of the capsules being inadvertently swallowed whole or in part and/or provide information on the associated risks if this occurs (e.g. if absorption of the drug is affected).
- Making improvements to the packaging to address the points that have been raised earlier above:
  - providing a designated area for a dispensing label on the bottle
  - improve the visibility of the strength presented on the capsule e.g. increasing the font size of the strengths

This report was produced in December 2019 using photographic images (not physical products) and packaging artwork of licensed Alkindi® that were available at the time of assessment. Images and artwork were obtained from the pharmaceutical company Diurnal Limited, the manufacturer of Alkindi®.

This report summarises product assessments undertaken by:
London Medicines Information Service (Northwick Park Hospital) and South West Medicines Information.
For comments email lnwh-tr.medinfo@nhs.net

The UKMI product safety assessment group would appreciate your views on the usefulness of this report. We have devised a short survey which we would appreciate you completing, it should take approximately 10 minutes to complete. Click the following link to complete the survey: https://www.surveymonkey.com/r/UKMiProductSafetyAssessments.

References

1) Scottish Medicines Consortium. Hydrocortisone 0.5mg, 1mg, 2mg and 5mg granules in capsules for opening (Alkindi®) (SMC2088). September 2018. Available at: https://www.scottishmedicines.org.uk/media/3758/hydrocortisone-granules-alkindi-final-september-2018-for-website.pdf

2) Summary of Product Characteristics. Alkindi 0.5mg, 1mg, 2mg, 5mg granules in capsules for opening. Diurnal Limited. Last updated on eMC: 13th February 2019. Available at: https://www.medicines.org.uk/emc/product/9032/smpc

3) Medicines and Health Regulatory Agency. Hydrocortisone muco-adhesive buccal tablets: should not be used off-label for adrenal insufficiency in children due to serious risks. Published 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

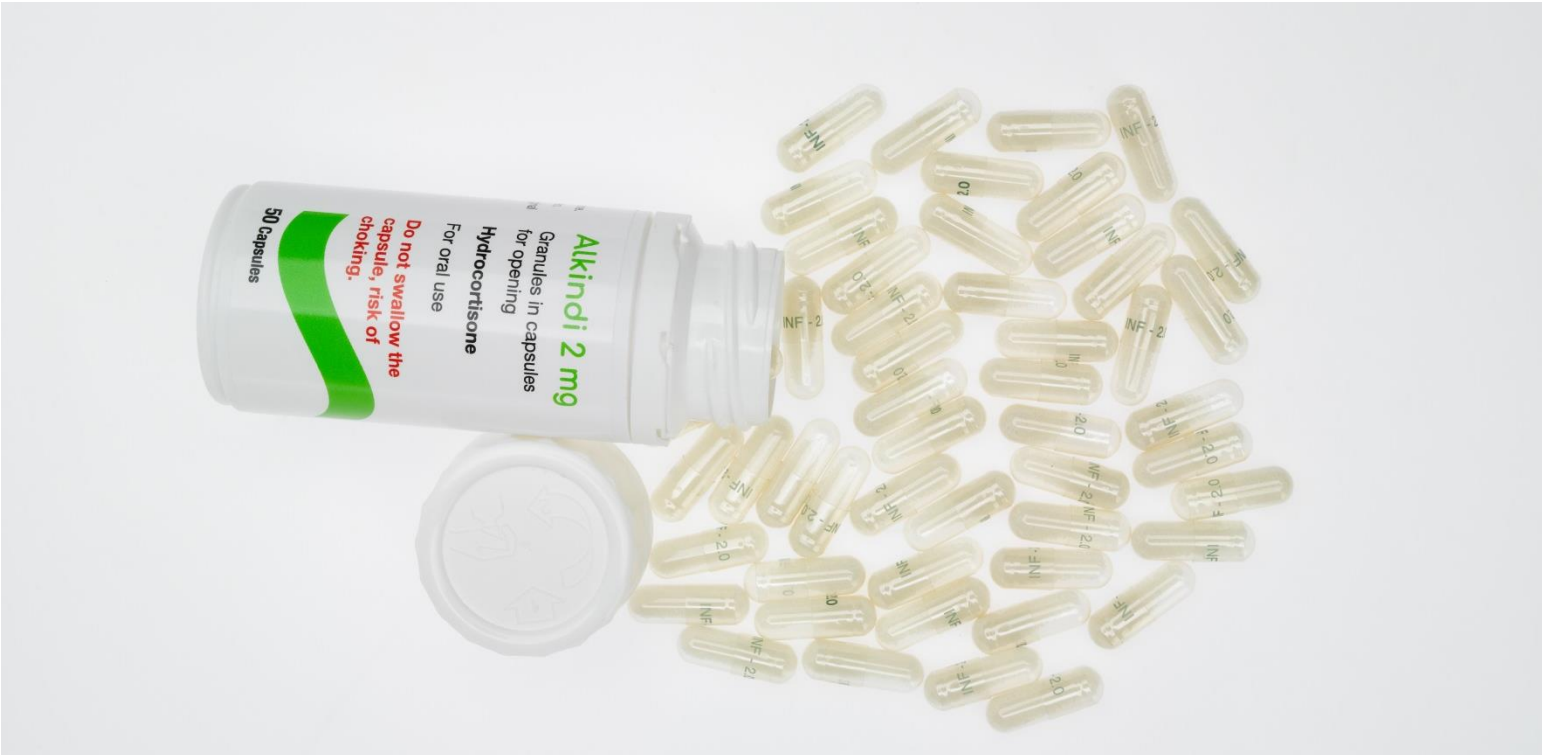
4) UKMi product assessment tool, full version. Accessed via https://www.sps.nhs.uk/articles/ukmi-product-assessment-tool/ on 08/05/2019

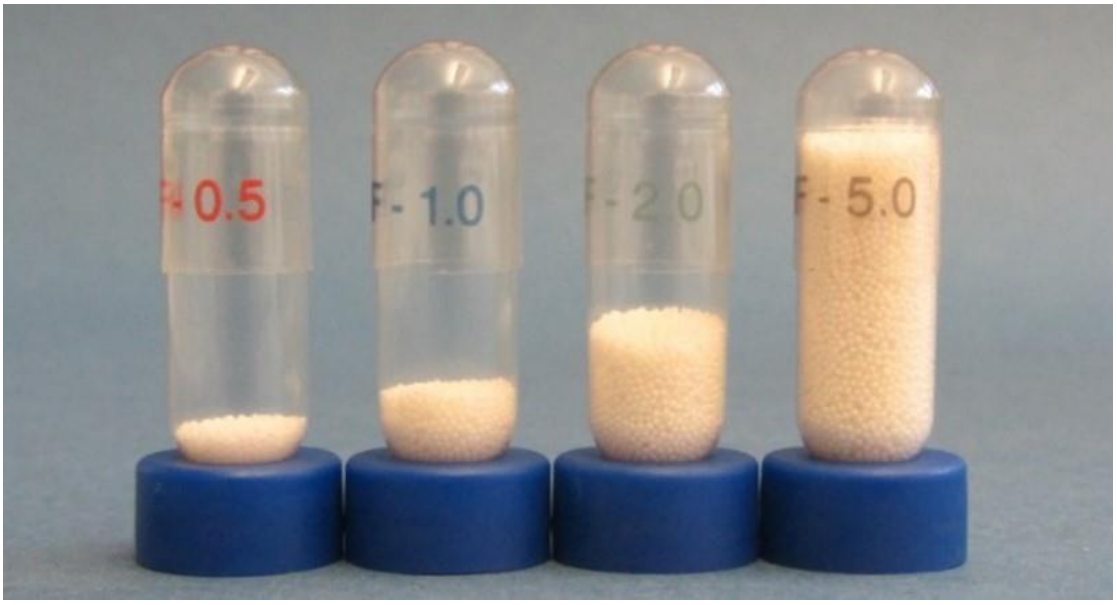
5) Patient Information Leaflet. Alkindi 0.5mg, 1mg, 2mg, 5mg granules in capsules for opening. Diurnal Limited. Last updated on eMC: 18th March 2019. Available at: https://www.medicines.org.uk/emc/product/9032/pil

6) European Medicines Agency Committee for Medicinal Products for Human Use. Summary of the European Public Assessment report for Alkindi. December 2017. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/alkindi

Product photos and artwork

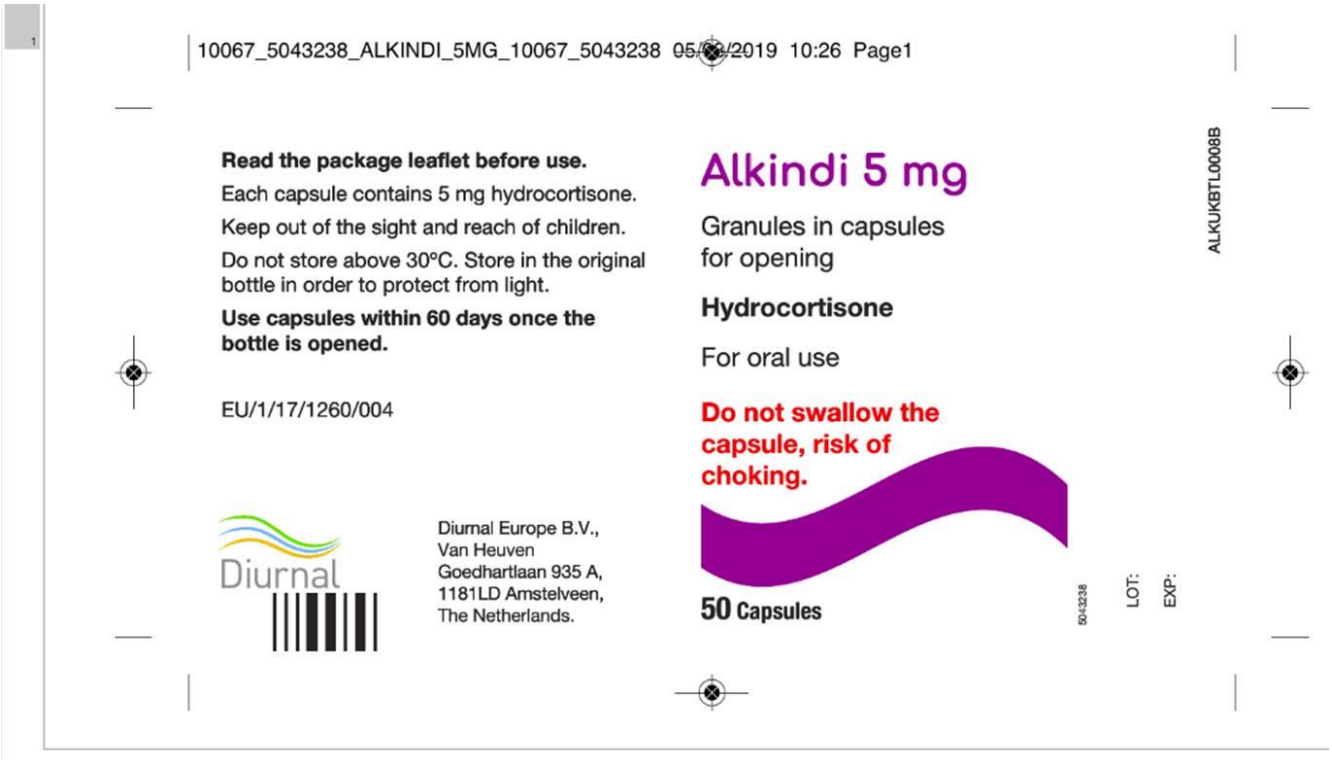
Overview of box, bottle and the capsules



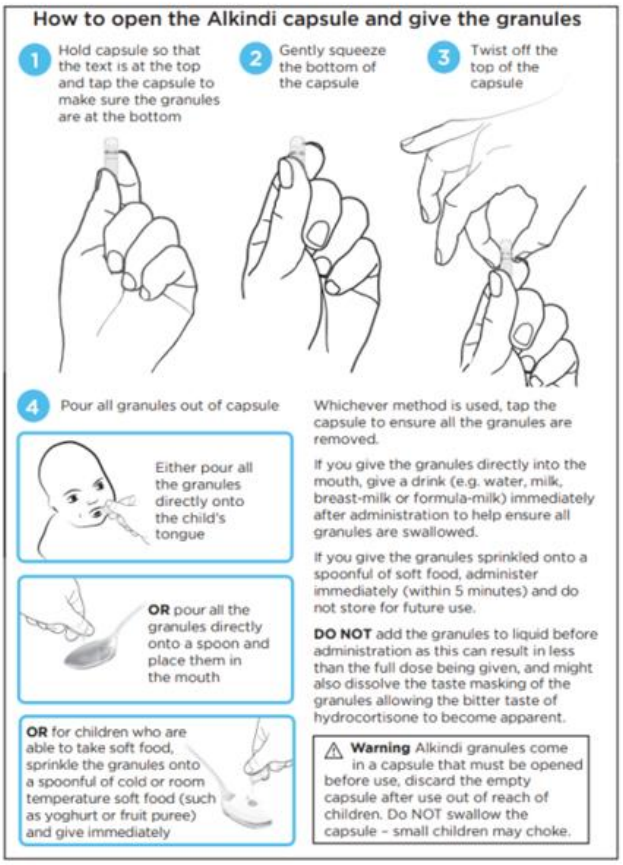

0.5
F - 1.0
F - 2.0
F - 5.0

Artwork of outer box

Artwork of bottle



Appendix A


How to open the Alkindi capsule and give the granules
1 Hold capsule so that the text is at the top and tap the capsule to make sure the granules are at the bottom
2 Gently squeeze the bottom of the capsule
3 Twist off the top of the capsule
4 Pour all granules out of capsule
Either pour all the granules directly onto the child's tongue
OR pour all the granules directly onto a spoon and place them in the mouth
OR for children who are able to take soft food, sprinkle the granules onto a spoonful of cold or room temperature soft food (such as yoghurt or fruit puree) and give immediately
Whichever method is used, tap the capsule to ensure all the granules are removed.
If you give the granules directly into the mouth, give a drink (e.g. water, milk, breast-milk or formula-milk) immediately after administration to help ensure all granules are swallowed.
If you give the granules sprinkled onto a spoonful of soft food, administer immediately (within 5 minutes) and do not store for future use.
DO NOT add the 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.
Warning Alkindi granules come in a capsule that must be opened before use, discard the empty capsule after use out of reach of children. Do NOT swallow the capsule – small children may choke.