Providers: ***(Surrey & Sussex NHS Foundations Trust, Royal Surrey County NHS Foundation Trust, Epsom & St Helier University Hospital NHS Trust, Kingston Hospital NHS Foundation Trust, Ashford & St Peter NHS Foundation Trust)*** **Commissioners** ***(East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG)***

Evidence review for consideration

This template should be completed when applying to either:

- Add a treatment onto a provider formulary OR
- Request consideration by the Prescribing Clinical Network for use where the treatment could potentially impact on primary and secondary care

Please ensure that all fields are completed and use the guidance notes within the template to formulate your review.

Please be aware that this consolidated review template is to ensure that any evidence review can be discussed at provider and commissioner level. This will ensure that there are minimal delays in any potential implementation.

Please ensure that you follow your organisations individual standard operating procedure for ensuring this evidence review is discussed at local level

Intervention details	
Name, brand name	Alkindi® Hydrocortisone granules in capsules for opening
Manufacturer	Diurnal Ltd
Proposed indication	Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old). Typically for use in <6 years old where the dose would have to be manipulated by crushing of 10mg tablets or production of special solution
Licensed status?	Licensed in those less than 18 years old
Requested by	Consideration by APC requested by Department of Paediatrics, Ashford and St Peter's Hospital. Use initiated by specialist in secondary care but would need to be used in primary care also for replacement therapy for ongoing maintenance therapy

SUMMARY

Clinical Effectiveness

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.[1]

The use of hydrocortisone buccal tablets given off-label is no longer recommended following MHRA advice in Drug Safety Update December 2018. [2] Yellow Card reports of off-label use of hydrocortisone muco-adhesive buccal tablets for adrenal insufficiency in children in the UK raised concerns about possible aggravation of congenital adrenal hyperplasia following substitution with muco-adhesive buccal tablets.
MHRA recommend that prescribers and pharmacists should only use available licensed hydrocortisone products for this condition.

There are also issues with using the 10mg hydrocortisone tablets for small doses.[1]

- **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.[3]

- **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.[3]

A study by Watson et al found that using hydrocortisone 10mg tablets for small doses put children being at risk of sub-optimal dosing.[4]

The SMC considered the product in September 2018 and produced a full review.[5]
SMC has accepted hydrocortisone granules for restricted use for the replacement therapy of adrenal insufficiency.
This acceptance is limited to 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.

Alkindi® is a hard capsule for opening, containing a single dose of granules.[6]

The study by Neumann et al[7] concluded that Infacort ® (development name of Alkindi®) was palatable, in a taste neutral formulation that was easy and convenient to administer.

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.

The Regional Medicines Optimisation (RMOC) London March 2019[8] were asked to provide advice on whether this formulation represented an efficacious, safe and cost-effective option. The Committee discussed the likely efficacy of this medicine. It was noted that there were no non-inferiority studies comparing Alkindi® to other hydrocortisone treatments. However, the papers presented to the Committee noted that the European Medicines Agency had not considered this necessary to licence a new formulation of hydrocortisone. As a result, the RMOC did not have any concern about the likely efficacy of this formulation.

The committee was unfortunately unable to provide advice on this topic and has referred it back to the MOPP**.** The RMOC website currently states that **"**Following publication of the revised operating model, NHS England Medicines and Diagnostic Policy team are exploring options for taking this topic forward. More information coming soon."

Safety

1. Specialist Pharmacy Service (SPS) in December 2019 produced an **In use product safety assessment report for Alkindi®** which summarises practical in-use safety considerations associated with its introduction.[9] The addition of this new product to the UK market with its unusual presentation 'granules in capsules for opening' raises some safety concerns.

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®. (Pictorial on administration instructions available in document)
- 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 is 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.

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.

2. Similar sounding name as Ayendi® - (diamorphine nasal spray)

3. Improved safety

MHRA have advised that hydrocortisone pellets (Corlan®) should not be used for hydrocortisone replacement therapy[2]

Alkindi® provides the advantage of allowing greater flexibility and accuracy in administering the appropriate hydrocortisone dose to paediatric patients in a licensed way without the need for compounding. The granules are also taste masked so the bitter taste of hydrocortisone does not cause difficulties with dosing/administration.[7]

Currently parents have to crush or disperse 10mg tablets leading to errors[4]

Patient impact	
PRIMARY CARE	This is a licensed product so should be easier to obtain as opposed to an unlicensed special. Also easier to give dose as does not require manipulation of 10mg tablets to get

SECONDARY CARE	dose- For use in secondary and primary care. Palatable, taste neutral formulation and easy and convenient to administer[6]
Cost implications	
PRIMARY CARE	Recommended replacement doses of hydrocortisone are 8 to 10mg/m2/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. For congenital adrenal hyperplasia (CAH) the dose is 9 to 15mg/m2/day typically in three divided doses, adjusted according to response. **Alkindi costs** *0.5mg £33.75 (50 capsules)* *1mg £67.50 (50 capsules)* *2mg £135.00 (50 capsules)* *(10mg tablets cost £9.08 for 30) January 2020 Drug Tariff* *Assuming dose of 1.5mg tds = £6.00 per day X 365=£2190 per patient per year but dose variable depending on individual patient requirements* *Up to 4 patients per year =£8760 per year (ASPH)* *Are there any savings from using the intervention?* No
SECONDARY CARE	
Relevant guidance / reviews	
SMC have reviewed and recommend use as first line in infants and young children with adrenal sufficiency from birth to 6 years for whom hydrocortisone would have to be individually prepared by manipulation of 10mg tablets or production of a special solution.	
Likely place in therapy relative to current treatments and suggested protocol for use (Primary & Secondary Care)	
For use in both primary and secondary care (in place of hydrocortisone 10mg tablets). To use for doses <5mg. Doses 5mg and above would use 10mg tablets	
Recommendation to Prescribing Clinical Network/Drugs & Therapeutics Committee/ New Drugs & Interface Groups	
Considered proposed formulary status at provider? **BLUE with information sheet**	

Colour classification guidelines

What action is needed to implement?

University Hospital Southampton is a specialist paediatric endocrinology centre and the recommendation on their joint formulary is

"Restricted for use only when standard tablets are not suitable or practical, e.g. infants/young children on doses <5mg.
UHS will only routinely stock lower strengths, i.e. 0.5mg, 1mg and 2mg.
Patients on doses ≥5mg should be switched to standard tablets, which can be divided using a tablet cutter.
Unlicensed in patients >18 years. Discuss options for adult patients unable to swallow tablets with pharmacist. "

It is recommended that APC makes a similar recommendation.

Equality Impact Assessment

Consider impact of the recommendations being made on the 9 protected characteristics (Equality Act 2010)

Protected Characteristic	No impact? (mark X against each characteristic that applies)	Positive impact? (mark X against each characteristic that applies)	Adverse (negative) impact? (mark X against each characteristic that applies)	If adverse (negative) impact, how can this be mitigated? (please add comments below)
Age		X		
Disability	X			
Gender reassignment	X			
Marriage & civil partnership	X			
Pregnancy & maternity	X			
Race	X			
Religion & belief	X			
Sex	X			
Sexual orientation	X			

Impact to primary care

May be easier to obtain from wholesalers than special solutions giving better availability at Community Pharmacies.

Impact to secondary care

PrescQIPP Hot Topics – Alkindi® September 2019[1] gives three worked examples for different doses of hydrocortisone comparing the use of Alkind® to liquid special or hydrocortisone 10mg tablets.
The cost pressure varies from 45% to 99% depending on the option used.

Consideration would still need to be given as to how to manage younger children where dose needed does not fit exactly with the strengths of Alkindi® available. In these cases a

liquid special may be more appropriate to prescribe. No difference in monitoring than hydrocortisone 10mg tablets or special solution. In Scotland, 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. However, there is currently no PAS price available in England in secondary care.
Impact to CCGs
Cost pressures in primary care would be the same as above. No difference in monitoring than hydrocortisone 10mg tablets or special solution

Intervention details	
Name and brand name	Alkindi® Hydrocortisone granules for opening
Licensed indication, formulation and usual dosage	Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old). Dosage must be individualised according to the response of the individual patient. Recommended replacement doses of hydrocortisone are 8-10 mg/m2/day for patients with adrenal insufficiency alone and 10-15 mg/m2/day in patients with congenital adrenal hyperplasia (CAH), typically in three or four divided doses. The granules must be given orally and should not be chewed. The capsule shell must not be swallowed but carefully be opened as follows: - The capsule is held so that the printed strength is at the top, and tapped to ensure all the granules are in the lower half of the capsule. - The bottom of the capsule is gently squeezed. - The top of the capsule is twisted off. - 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. 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. - Whichever method is used, the capsule is tapped to ensure all the granules are removed. Immediately after administration a drink such as water, milk, breast-milk, or formula-milk should be given to help ensure all granules are swallowed. If the granules are sprinkled onto a spoonful of soft food this should be given immediately (within 5 minutes) and not stored for future use.[4]
Complex calculation	Dosage must be individualised according to the response of the individual patient. Calculations are based on body surface area.

Summary of mechanism of action, and relevant pharmacokinetics	Include brief summary of pharmacology, and relevant pharmacokinetics Hydrocortisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally-occurring and synthetic, which are readily absorbed from the gastro-intestinal tract. Hydrocortisone is believed to be the principal corticosteroid secreted by the adrenal cortex. Naturally-occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Following oral administration, hydrocortisone is rapidly absorbed from the gastro-intestinal tract and the oral Alkindi was approximately 87 % bioavailable. 90% or more of circulating hydrocortisone is reversibly bound to protein (glycoprotein and albumin) Hydrocortisone is metabolised in the liver and mainly conjugated (as glucuronides,) and a very small proportion of unchanged hydrocortisone is excreted in the urine, The terminal half-life of hydrocortisone is about 1.5 hours
Therapeutic risk	There is a significant risk of patient harm if the intervention is not used as intended.
Total number of product risk factors (For injectable products only)	Not applicable
Important drug interactions	Hydrocortisone is metabolised by cytochrome P450 3A4 (CYP3A4). Concomitant administration of medicinal products that are inhibitors or inducers of CYP3A4 may therefore lead to unwanted alterations in serum concentrations of Alkindi with the risk of adverse effects, particularly adrenal crisis. The need for dose adjustment when such medicinal products are used can be anticipated and patients should be closely monitored.[6]
Side effects	Include information from SPC [6] Psychosis with hallucinations and delirium Mania Euphoria Gastritis Nausea Hypokalaemic acidosis as reported in the scientific literature in adult patients for other hydrocortisone medicinal products when given as adrenal insufficiency replacement therapy with frequency not known
Precautions	Include information from SPC[6] <u>Adrenal crisis</u> Where a child is vomiting or acutely unwell parenteral hydrocortisone should be started without delay, carers should be trained in adminstering this in an emergency. Sudden discontinuation of therapy with Alkindi risks triggering an adrenal crisis and death. Replacement schedules of corticosteroids for people with adrenal insufficiency do not cause immunosuppression and are not, therefore, contraindications for administration of live vaccines. Infection should not be more likely at a replacement dose of

	hydrocortisone, but all infections should be treated seriously and stress dosing of steroid initiated early. Patients with adrenal insufficiency are at risk of life-threatening adrenal crisis during infection so clinical suspicion of infection should be high and specialist advice should be sought early. <u>Undesirable effects of corticosteroid replacement therapy</u> Most undesirable effects of corticosteroids are dose and duration of exposure related. Undesirable effects are therefore less likely when using corticosteroids as replacement therapy. Corticosteroids may cause growth retardation in infancy, childhood and adolescence; this may be irreversible. Excessive weight gain with decreased height velocity or other symptoms or signs of Cushing syndrome indicate excessive glucocorticoid replacement. Infants require frequent assessment and should be evaluated at a minimum every 3 to 4 months to assess growth, blood pressure, and general well-being. Bone mineral density may be impacted in children when higher doses of replacement steroids are used. The lowest appropriate dose of steroid according to the response of the individual patient should be used. Patients/and or carers should be warned that potentially severe psychiatric adverse reactions; euphoria, mania, psychosis with hallucinations and delirium have been seen in adult patients at replacement doses of hydrocortisone Risks may be higher with high doses/systemic exposure although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroids, especially when a patient has a history of allergies to medicinal products. <u>Visual disturbance</u> Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy which have been reported after use of systemic and topical corticosteroids. <u>Excretion of granules</u> The granules may sometimes be seen in stools since the centre of the granule is not absorbed in the gut after it has released the active substance. This does not mean the medicinal product has been ineffective and the patient should not take another dose for this reason.

Contraindications	Include information from SPC[6] Hypersensitivity to the active substance or to any of the excipients. Patients with dysphagia or premature infants where oral feeding has not been established <u>Nasogastric tube feeding</u> Alkindi granules are not suitable for nasogastric administration as they may cause tube blockage.
Pregnancy & Lactation	Hydrocortisone for replacement therapy can be used during pregnancy Hydrocortisone for replacement therapy can be used during breast-feeding[6] However not applicable in proposed age group
Monitoring requirements	Include any relevant information on monitoring requirements either for efficacy or toxicity Same monitoring for adrenal function as with hydrocortisone 10mg tablets
Prescribing considerations	• Likely traffic light status (see attached guidelines) **BLUE** with information sheet  Colour classification guidelines
Other considerations	For routine care 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. Store in the original bottle in order to protect from light. Shelf life after first opening: 60 days[6] Similar sounding name as Ayendi® - diamorphine nasal spray

Potential patient group (if appropriate to include)	
Brief description of disease	Include disease severity, morbidity and mortality, prognosis
Potential patient numbers per 100,000	Describe number of patients affected and potential number of patients likely to receive the treatment
Patient outcomes required	Describe desired treatment benefits, and what outcomes/benefits, and size of effect are considered clinically significant

Summary of current treatment pathway
To use in place of 10mg hydrocortisone tablets where dose would have to be manipulated by crushing of 10mg tablets or production of special solution so reduced error of dosing

Evidence review
SMC have reviewed and recommend use as first line in infants and young children with adrenal sufficiency from birth to 6 years for who hydrocortisone would have to be individually prepared by manipulation of 10mg tablets or production of a special solution[5]

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	
Recommendations from national / regional decision making groups	SMC have reviewed and recommend use as first line in infants and young children with adrenal sufficiency from birth to 6 years for who hydrocortisone would have to be individually prepared by manipulation of 10mg tablets or production of an unlicensed special solution, or hydrocortisone given off-label buccal tablets[5]
Stakeholder views	Use the enclosed proforma to obtain views from clinicians Summarise who has been consulted e.g. secondary care consultants, what their views are and any declared conflict of interest Have views of patient groups been sought? Dr S Bahl , consultant paediatrician, ASPH
CCG priorities	To use in place of 10mg hydrocortisone tablets where dose would have to be manipulated by crushing of 10mg tablets or production of special solution.

Health economic considerations	
Cost per year per patient	Assuming dose of 1.5mg tds = £6.00 per day X 365=£2190 per patient per year but dose variable depending on individual patient requirements
Alternative treatments cost per patient per year	See PrescQIPP document for alternative costing examples[1]
Other financial considerations (if relevant)	NONE
Health economic data (if available)	Include information from relevant health economic analysis, indicate the level of robustness of the analysis

References

Include references written in Vancouver style

1. PrescQIPP Hot Topic Alkindi® Hydrocortisone 0.5mg, 1mg, 2mg and 5mg granules in capsules for opening September 2019
2. Drug Safety Update volume 12, issue 5: December 2018: 5.
3. 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
4. Watson et al. int.J.Pharm 2018, Jul 10;545(1-2):57-63
5. Scottish Medicines Consortium 3rd September 2018 https://www.scottishmedicines.org.uk/medicines-advice/hydrocortisone-alkindi-fullsub-smc2088/
6. SPC Alkindi accessed 02.01.20 https://www.medicines.org.uk/emc/product/9032/smpc
7. U. Neumann et al. Clinical Endocrinology, 2018;88-21-29 :Absorption and tolerability of taste-masked hydrocortisone granules in neonates, infants and children under 6 years of age
8. Regional Medicines Optimisation Committee London Minutes of March 2019 meeting available at https://www.sps.nhs.uk/wp-content/uploads/2019/02/Final-Minutes-London-RMOC-March-19.pdf
9. Specialist Pharmacy Service. In use product safety assessment report for Alkindi® (hydrocortisone) granules in capsules for opening. 19th December 2019. Available at https://www.sps.nhs.uk/articles/in-use-product-safety-assessment-report-for-alkindi-granules-in-capsules-for-opening/

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Declaration of Interest:

None

Date: 8/4/19

Reviewed by:

Lis Stanford, Acting Head of Medicines Management, North West Surrey CCG (2.1.20)

Declaration of Interest:

None

Date: 2.1.20

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
v.1	*8/4/19*	*D.Hopper*		*DTC application*

v.2	*2/1/20*	*Lis Stanford*		*Additions for consideration by APC*