Part VI: Summary of the risk management plan

Summary of risk management plan for Alkindi® (Hydrocortisone Granules in Capsules for opening)

This is a summary of the risk management plan (RMP) for Alkindi. The RMP details important risks of Alkindi, how these risks can be minimised, and how more information will be obtained about Alkindi's risks and uncertainties (missing information).

Alkindi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Alkindi should be used.

This summary of the RMP for Alkindi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Alkindi's RMP.

I. The medicine and what it is used for

Alkindi is authorised for replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to <18 years old). It contains Hydrocortisone as the active substance and it is given by mouth.

Further information about the evaluation of Alkindi's benefits can be found in Alkindi's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004416/human_med_002221.jsp&mid=WC0b01ac058001d124.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Alkindi together with measures to minimise such risks and the proposed studies for learning more about Alkindi's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Alkindi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Alkindi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Alkindi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risks	Growth Retardation Acute Psychiatric Effects Reduced Bone Mineral Density and Risk of Bone Fractures Drug-drug interactions (with CYP3A4 enzyme inducers and CYP3A4 inhibitors)
Important potential risks	Choking on the capsule Accidental Underdose Aspiration of Granules Drug-drug interactions seen only at high doses of Hydrocortisone (with aspirin, coumarins, diuretics, anti-hypertensives, drugs or substances causing hypokalaemia, hypoglycaemic agents) Risk of Central Serous Chorioretinopathy
Missing information	Long Term Use in Paediatric Patients Use in Hepatic Impairment Use in Renal Impairment

II.B Summary of important risks

Important identified risk: **Growth Retardation**	
Evidence for linking the risk to the medicine	Growth retardation has been well recognised in children on chronic steroids and is dose-related. The situation in adrenal insufficiency may be complicated by the underlying disease and/or comorbidities. In congenital adrenal hyperplasia an initial phase in the first six months of life of relative insensitivity to androgens is followed by androgen sensitivity where growth can be accelerated by androgen excess, however this is accompanied by bone age acceleration leading to precocious puberty, early fusion of epiphyses and compromised final height. Conversely, overdose of steroids will suppress this androgen effect but cause growth retardation. Some studies, but not all, suggest that steroid dose in the first two years of life is critical to final height. In secondary adrenal insufficiency due to pituitary dysfunction, ACTH deficiency is often accompanied by growth hormone deficiency which will impact height regardless of the appropriateness of steroid dose. Growth hormone supplementation can improve final height expectation, but it may be difficult to disentangle the various factors affecting growth. Despite a progressive reduction in steroid dosing seen since the introduction of steroid therapy for CAH in the 1950s, even recent cohort studies at doses close to the guidance range seem to have an effect on final height.
Risk factors and risk groups	The effect on final height appears to be limited to patients with CAH. The evidence from historical cohorts is equivocal as to whether this is associated with hydrocortisone dose, fludrocortisone dose or both. There are no studies showing a final height impact on patients with Addison's disease. With hypopituitarism the picture is complicated by other pituitary hormone deficiencies that may affect growth- notably Growth Hormone Deficiency
Risk minimisation measures	Routine risk minimisation measures Routine risk communication: Text in SmPC section 4.2 includes European Society of Paediatric Endocrinology dosing guidance and monitoring guidance, section 4.4 and PIL further information related to the risk.

Important identified risk: **Acute Psychiatric Effects**	
Evidence for linking the risk to the medicine	Psychosis is a well-known phenomenon with chronic high dose steroid use. Commoner still is euphoria on first starting therapeutic doses of steroids. There have also been reports of suicidal ideation with steroids. In general, the psychiatric effects of steroids have been thought to be dose-related and so of less relevance to replacement therapy. Although a few important case reports of psychiatric symptoms in adults on replacement doses of hydrocortisone- summarised in a paper from 2015, have been seen, these effects have not been seen in paediatric patients. A brief literature review describes two cases of manic episodes, four cases of overt psychotic symptoms with hallucinations and one report of delirium. Reassuringly, the effects seen in adults were limited in duration and reversed with reduction in replacement steroid dose.
Risk factors and risk groups	Reactions are seen most often at initiation or withdrawal of therapy. Reactions such as agitation or euphoria commonly seen in therapeutic use and effects seem to be dose related, but have been seen in adults occasionally at initiation of replacement dose.
Risk minimisation measures	Routine risk communication: Text in SmPC section 4.4 and PIL communicating risk and management and 4.8 communicating specific symptoms

Important identified risk: **Reduced Bone Mineral Density and Risk of Bone Fractures**	
Evidence for linking the risk to the medicine	Cohorts of adult patients with congenital adrenal hyperplasia have been shown to have lower bone mineral density than age and sex matched controls, though this is not seen in all cohorts. These differences seem to be height dependant though studies in patients on replacement levels of hydrocortisone seem to show no clear correlation with steroid dose, with other factors such as dehydroepiandrosterone sulfate (DHEAS) levels being implicated. Overall our understanding of the nature of bone mineral density changes in CAH is evolving, but bone mineral density should be monitored and glucocorticoid dose kept to the minimum necessary. Appropriate advice is included in the proposed SmPC. Pharmacovigilance can help improve our understanding of the inter-relationship, if any, between replacement steroids and bone mineral density.
Risk factors and risk groups	Patients with CAH seem to be at higher risk of reduced bone mineral density than patients with other forms of adrenal insufficiency, perhaps reflecting the relative doses of glucocorticoids used in these populations. Female patients seem to be at higher risk of fracture than controls, though this has not been shown in a male population.

	Dexamethasone usage may increase the risk over other replacement glucocorticoid regimens. Other recognised causes of reduced bone density may increase risk further e.g. immobility.
Risk minimisation measures	Routine risk communication: Text in SmPC section 4.2 includes European Society of Paediatric Endocrinology dosing guidance and monitoring guidance, section 4.4 and PIL further information related to the risk.

Important identified risk: **Drug-drug interactions (with CYP3A4 enzyme inducers and CYP3A4 inhibitors)**	
Evidence for linking the risk to the medicine	Hydrocortisone is a drug substance for which considerable experience of use in man is available, and the body of scientific knowledge is based on a combination of literature references from published pharmaco-toxicological information including scientifically accepted monographs and clinical trials, along with results of post-marketing experience gained by widespread clinical use. However much of the data described is from high dose usage and is not relevant at replacement doses. In replacement use there are only a few case reports of interactions. Interaction with Phenytoin was described in a child with AI requiring hydrocortisone dose increase. Interaction with Oxcarbazepine was described in an adolescent with AI requiring Hydrocortisone dose increase. In adults interaction with Rifampicin has been described causing increased metabolism of hydrocortisone leading to crisis. Finally in adults Grapefruit Juice and Liquorice have been found to increase cortisol availability through CYP3A4 inhibition. Although the main component of Liquorice, Glycyrrhizin, has no effect on CYP3A4, other constituents particularly (3R)-vestitol, 4-hydroxyguaiacol apioglucoside and liquiritigenin 7,4'-diglucoside are potent CYP3A4 inhibitors. From the literature therefore it can be expected that known CYP3A4 inhibitors or inducers will affect hydrocortisone requiring potential dose adjustment.
Risk factors and risk groups	Most children, unlike older adults do not suffer from multiple co-morbidities and so tend to be on one or few drugs only. However some children with severe congenital conditions, or those with syndromic causes of adrenal insufficiency may have several organ systems involved and so be at higher risk of being on multiple medicines.
Risk minimisation measures	Routine risk communication: Text in SmPC section 4.5 and PIL delineating interactions and specific examples of medicines in class.

Important potential risk: **Choking on the capsule**	
Evidence for linking the risk to the medicine	Potential only- no incidents of this occurring, and no data to suggest this happens currently with compounded hydrocortisone that is traditionally dispensed in capsules.
Risk factors and risk groups	Children with carers with learning difficulties or limited literacy in the language used on the patient information leaflet accompanying the pack (e.g. First generation immigrants).
Risk minimisation measures	Text in SmPC section 4.2 and PIL explaining that capsule is carrier only and should not be administered.

Important potential risk: **Accidental Underdose**	
Evidence for linking the risk to the medicine	Granules were retained in adult studies Infacort001 and 003 and paediatric study Infacort003. None of these were significant in terms of drug dose (maximum 0.04mg). Instruction to tap the capsule was introduced and no episodes of granule retention have been reported in the ongoing study Infacort004.
Risk factors and risk groups	Children with carers with limited vision
Risk minimisation measures	Text in SmPC section 4.2 and PIL explaining the administration, diagram in PIL explaining administration.

Important potential risk: **Aspiration of Granules**	
Evidence for linking the risk to the medicine	No evidence of this risk during clinical development process or clinical trials in neonates.
Risk factors and risk groups	Premature infants, infants/children with dysphagia
Risk minimisation measures	Text in SmPC section 4.2 and PIL explaining the administration, text in SmPC 4.3 stating contraindication in dysphagia or in premature neonates where oral feeds are not tolerated, diagram in PIL explaining administration.

Important potential risk: **Drug-drug interactions seen only at high doses of Hydrocortisone (with aspirin, coumarins, diuretics, anti-hypertensives, drugs or substances causing hypokalaemia, hypoglycaemic agents)**	
Evidence for linking the risk to the medicine	Hydrocortisone is a drug substance for which considerable experience of use in man is available, and the body of scientific knowledge is based on a combination of literature references from

	published pharmaco-toxicological information including scientifically accepted monographs and clinical trials, along with results of post-marketing experience gained by widespread clinical use. Examples of the medicines implicated would be Aspirin Coumarin anticoagulants e.g. Warfarin Diuretics e.g. Acetazolamide, loop diuretics e.g. Frusemide, thiazides e.g. Indapamide, Bendroflumethiazide Chlortalidone Xipamide Metolazone Anti-hypertensives e.g. Beta-blockers (e.g. Propranolol, Oxprenolol, Sotalol, Labetalol), Alpha blockers (e.g. Doxazosin, Indoramin, Prazosin, Terazosin) Calcium channel blockers (e.g. Verapamil, Diltiazem, Amlodipine, Nifedipine), Clonidine, Diazoxide, Methyldopa, Moxonidine, Nitrates (e.g. Glyceryl Trinitrate, Isosorbide Dinitrate), Nitroprusside, Hydralazine, Minoxidil, Guanethidine, ACE inhibitors (e.g. Captopril, Enalapril maleate, Ramipril), Angiotensin II receptor antagonists (e.g. Azilsartan medoxomil, Losartan potassium, Valsartan) Drugs or substances causing hypokalaemia e.g. Cardiac Glycosides (e.g. Digoxin), Diuretics (e.g. Frusemide), beta2 sympathomimetics (e.g. Salbutamol), Amphotericin). Hypoglycaemic agents e.g. (e.g. Insulin- human and porcine/bovine, Glibenclamide, Gliclazide, Glimepiride, Glipizide, Tolbutamide, Nateglinide, Repaglinide).
Risk factors and risk groups	Patients with 11β hydroxylase deficiency leading to CAH often present with hypertension and so may be on anti-hypertensives, however these interactions have not been described at replacement doses of hydrocortisone
Risk minimisation measures	Text in SmPC section 4.1 Alkindi is indicated for replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to <18 years old).

Important potential risk: **Risk of Central Serous Chorioretinopathy**	
Evidence for linking the risk to the medicine	Long term pharmacovigilance data on steroids has revealed an association between usage of steroids and a rare form of eye disease; chorioretinopathy
Risk factors and risk groups	This association has been seen with all forms of steroids including inhaled and topical and appears to be more likely with higher doses of steroid therapy.
Risk minimisation measures	Text in SmPC section 4.4 and PIL

Missing information: **Long Term Use in Paediatric Patients**	
Risk minimisation measures	None

Missing information: **Use in Hepatic Impairment**	
Risk minimisation measures	None

Missing information: **Use in Renal Impairment**	
Risk minimisation measures	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

N/A

II.C.2 Other studies in post-authorisation development plan

N/A