14 December 2017
EMA/4145/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alkindi

International non-proprietary name: hydrocortisone

Procedure No. EMEA/H/C/004416/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ACTH Adrenocorticotropin

ADME Absorption, distribution, metabolism and excretion

AhR Aryl hydrocarbon receptor

AI Adrenal insufficiency

ARNT AhR Nuclear Translocator

AUC_{0-t} area under the concentration-time curve from the time of dosing to the time of the last observed concentration

AUC_{0-inf} area under the concentration-time curve extrapolated to infinity from dosing time, based on the last observed concentration

$AUMC_{0-t}$ area under the first moment curve from time 0 to the time of last observed concentration

$AUMC_{0-inf}$ area under the first moment curve from time 0 extrapolated to infinity

BCS Biopharmaceutical classification system

Bw Body weight

CAH Congenital adrenal hyperplasia

CBG Cortisol-binding globulin

CEP Certificate of Suitability of the EP

CHMP Committee for Medicinal Products for Human Use

CI Confidence interval

CL/F Clearance

C_{max} Maximum concentration

CRH Cortico-releasing hormone

CRO Contact Research Organisation

CV% Coefficient of variation

CVMP Committee for Veterinary Medicinal Products

EDQM European Directorate for the Quality of Medicines

EMA European Medicines Agency

EU European Union

GC Gas Chromatography

GCLP Good Clinical Laboratory Practice

GCP Good Clinical Practice

GLP Good Laboratory Practice

GLUT4 Glucose transporter type 4

GR Glucocorticoid receptor

GRAS Generally Recognized As Safe

GRE Glucocorticoid response elements

HDPE High Density Polyethylene

HPA Hypothalamic-pituitary-adrenal

HPLC High performance liquid chromatography

hr Hour

11β-HSD2 11β-hydroxysteroid dehydrogenase type 2

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP Inductively coupled plasma

IMP Investigational medicinal product

IPC In-process control

IR Infrared

IRHC Immediate release hydrocortisone

JP Japanese Pharmacopoeia

LD50 Lethal dose in 50% of sample

LS mean Least square mean

MALB Microalbuminuria

MAT mean absorption time (calculated as oral MRT_{0-inf} - i.v. MRT_{0-inf} of hydrocortisone)

MRT_{0-t} mean residence time from time 0 to the time of last observed concentration

MRT_{0-inf} mean residence time from time 0 extrapolated to infinity

NC Not calculated

NOEL No Observed Effect Level

PAI Primary adrenal insufficiency

PE Polyethylene

Ph. Eur. European Pharmacopoeia

PD Pharmacodynamics

PDCO Paediatric committee

PIP Paediatric investigation plan

PK Pharmacokinetics

PL Product Licence

POPPK Population pharmacokinetics

PP Polypropylene

PUMA Paediatric use marketing authorisation

PVP polyvinylpyrrolidone

QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
SD	Standard deviation
SGF	simulated gastric fluid
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half-life
TAMC	Total Aerobic Microbial Count
t_{max}	The time to C_{max} during a dosing interval
TH	Tyrosine hydroxylase
TYMC	Total Combined Yeasts/Moulds Count
UAC	Urine albumin/creatinine ratio
UPC	Urine protein/creatinine ratio
USP	United States Pharmacopoeia
UV	Ultraviolet
Vss	Distribution at steady state
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant DIURNAL LTD submitted on 25 November 2016 an application for a Paediatric Use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Alkindi, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 1 April 2016.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Alkindi is indicated in neonates, infants and children less than 6 years.

- For use as replacement therapy in primary, secondary, or acute adrenal insufficiency.
- Pre-operatively, and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenal reserve.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and two bioequivalence studies with the reference medicinal product Hydrocortisone Auden Mckenzie instead of non-clinical and clinical studies unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Hydrocortisone Tablets, 10mg, tablets.
- Marketing authorisation holder: Auden Mckenzie (Pharma Division) Ltd.
- Date of authorisation: 03 February 1989
- Marketing authorisation granted by:
  - Member State (EEA) : United Kingdom
- Marketing authorisation number: PL 17507/0246

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Hydrocortisone Tablets
- Marketing authorisation holder: Auden Mckenzie (Pharma Division) Ltd
- Date of authorisation: 03 February 1989
- Marketing authorisation granted by:

- Member State (EEA): United Kingdom
- Marketing authorisation number: PL 17507/0246

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Hydrocortisone Tablets, 10mg, tablets.
- Marketing authorisation holder: Auden Mckenzie (Pharma Division) Ltd.
- Date of authorisation: 03 February 1989
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
  - Marketing authorisation number(s): PL 17507/0246

Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0031/2013 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP EMEA-001283-PIP01-12 was completed.

The PDCO issued an opinion on compliance for the PIP EMEA-C-001283-PIP01-12.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Koenraad Norga Co-Rapporteur: Kolbeinn Gudmundsson

- The application was received by the EMA on 25 November 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 23 March 2017.

- During the meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 3 August 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 September 2017.
- During the PRAC meeting on 28 September 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 12 October 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 7 November 2017.
- During the meeting on December 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Alkindi on 14 December 2017.

2. Scientific discussion

2.1. Introduction

The reference medicinal product for Alkindi is Hydrocortisone Tablets, 10 mg (United Kingdom) – PL 17507/0246 (1989).

In indication of the reference medicinal product is the following:

"Corticosteroid.

For use as replacement therapy in primary, secondary, or acute adrenocortical insufficiency.

Preoperatively, and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenocortical reserve. "

The main differences in Alkindi compared to the reference medicinal product are:

- Change in pharmaceutical form
- Change in strength
- Indication in replacement therapy in paediatric patients **only**.

The present hybrid **application** for a PUMA (Paediatric use marketing authorisation) concerns **a paediatric-specific formulation (granules in capsules for opening)** of immediate-release hydrocortisone (IRHC).

The initial indication claimed by the Applicant was "for treatment of the 0-6 year patient group". Upon request of the CHMP the indication has been widened to contain the full paediatric population (from birth to <18 years old).

The clinical development plan for Alkindi comprised of two key components: (1) an investigation of the safety and pharmacokinetic (PK) profile of Alkindi **in adults** to ascertain the exposure and optimal dosing in the target paediatric population and **to establish bioequivalence to the current standard IRHC**, and (2) an investigation of cortisol levels after dosing with Alkindi in the target paediatric population with reference to the established PK and pharmacodynamic (PD) knowledge already in place for the use of hydrocortisone in the AI indication and palatability in the 0-6 years patient group.

The initially proposed therapeutic indication was (identical to the reference medicinal product):

"Alkindi is indicated in neonates, infants and children less than 6 years.

- *For use as replacement therapy in primary, secondary, or acute adrenal insufficiency.*
- *Pre-operatively, and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenal reserve."*

During the procedure the CHMP has suggested that a more simplified wording of the therapeutic indication could be agreed and proposed the *"Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old)."* The CHMP considered that *"preoperatively, and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenocortical reserve"* included in the wording of the indication of the reference medicinal product is covered by "*replacement therapy of adrenal insufficiency"* wording of the indication.

Also, the applicant has addressed the extrapolation of the available data for the initial claim of the indication to the group of children > 6 years (see Conclusions on clinical efficacy section of this report). The CHMP agreed with the extrapolation exercise and that the product could be indicated in the entire age spectrum of the paediatric population. The following indication was approved for Alkindi:

"Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old)."

2.1.1. Disease or condition

Primary adrenal insufficiency (PAI) is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids. PAI is a severe and potentially life-threatening condition due to the central role of these hormones in energy, salt, and fluid homeostasis. Cortisol deficiency results in a decrease in feedback to the hypothalamic-pituitary axis and subsequent enhanced stimulation of the adrenal cortex by elevated levels of plasma ACTH. The signs of PAI are mainly based on the deficiency of gluco- and mineralocorticoids and the **resultant weight loss, orthostatic hypotension due to dehydration, hyponatremia, hyperkalemia, changes in blood count (anemia, eosinophilia, lymphocytosis), and hypoglycaemia**.

The most common cause of PAI is **autoimmunity** (up to 90% in Western countries), followed by **infectious diseases such as tuberculosis, adrenalectomy, neoplasia, and various genetic causes**; the last are more likely to be present and diagnosed in children. In fact, the non-autoimmune cases of PAI are more frequently seen among children and the elderly and **congenital adrenal hyperplasia (CAH)** due to 21-

hydroxylase deficiency is the most common cause of adrenal insufficiency in infancy (Bornstein et al., 2016; Speiser et al., 2010). This is reflected in the patient group recruited for the pivotal Infacort trial, where 23/24 patients presented with CAH.

2.1.2. Epidemiology

Primary adrenal insufficiency PAI is a rare disease with a reported prevalence of about 100 to 140 cases per million and an incidence of 4:1 000 000 per year in Western societies (Bornstein et al., 2016).

2.1.3. Clinical presentation, diagnosis

Except for **salt craving**, the symptoms of PAI are rather nonspecific and include weakness, fatigue, musculoskeletal pain, weight loss, abdominal pain, depression, and anxiety. As a result, the diagnosis is frequently delayed, resulting in a clinical presentation with an acute life-threatening adrenal crisis (Bornstein et al., 2016).

Considering the proposed therapeutic indication, **most paediatric patients will suffer from CAH due to genetic mutations**, and genetic screening is an appropriate tool for early diagnosis, which greatly reduces the time to diagnosis, morbidity and mortality. **The death rate in salt-wasting CAH without screening is between 4-10%** (Speiser et al., 2010).

2.1.4. Management

Immediate release hydrocortisone is the standard of care therapy in PAI and CAH. The goal of therapy is to **reduce excessive androgen secretion** by replacing the deficient hormones. Proper treatment with glucocorticoids (GCs) prevents adrenal crisis and virilization, allowing normal growth and development. Clinical management of classic CAH is **a difficult balance between hyperandrogenism and hypercortisolism**.

Under treatment carries **the risk of adrenal crisis** and allows increased adrenal androgen production, with accelerated bone age and loss of growth potential; **overtreatment may suppress growth, increase blood pressure, and cause iatrogenic Cushing's syndrome**.

Recent clinical practice guidelines have been published by the endocrine society (Bornstein et al., 2016; Speiser et al., 2010).

An unmet need was identified, by the PDCO, for an age-appropriate oral formulation for hydrocortisone for the treatment of PAI in the 0-2 years age group.

2.1.5. About the product

Alkindi formulation is **coated granules containing the active substance hydrocortisone**. The granules are provided with a coating for masking of the bitter taste of the active substance. Granules are provided in **hard capsules containing 0.5, 1, 2 or 5 mg hydrocortisone coated granules**. **The capsules are not for consumption.** These presentations and novel formulation should sustain a precise dosing for use in the target population of patients 0-6 years of age.

The pharmaceutical form is granules in capsules for opening.

2.1.6. The development programme / Compliance with CHMP guidance / Scientific advice

No formal scientific advice was requested prior to the initiation of the clinical development program. The clinical program was based on the PIP developed in collaboration with the PDCO (EMEA-001283-PIP01-12). The plan includes **a bioequivalence study in healthy adults** to compare the newly developed granule formulation to the marketed tablet formulation and **a single-dose pharmacokinetics and palatability study in infants and children less than 6 years of age**. A PIP waiver was granted for the paediatric population from 6 years to less than 18 years. PIP compliance was confirmed in 2016 by the PDCO.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release granules in capsules for opening containing 0.5 mg, 1.0 mg, 2.0 mg or 5.0 mg of hydrocortisone as active substance.

Other ingredients are:

Capsule contents: microcrystalline cellulose, hypromellose, magnesium stearate and ethyl cellulose.

Capsule shell: hypromellose.

Printing ink:

0.5 mg capsules: shellac, propylene glycol, concentrated ammonia solution, potassium hydroxide, red iron oxide (E172).

1 mg capsules: shellac, propylene glycol, concentrated ammonia solution, indigotine (E132).

2 mg capsules: shellac, propylene glycol, concentrated ammonia solution, indigotine (E132), yellow iron oxide (E172), titanium dioxide (E171).

5 mg capsules: shellac, propylene glycol, concentrated ammonia solution, potassium hydroxide, titanium dioxide (E171), black iron oxide (E172).

Each hard capsule for opening contains a single dose of granules. The capsules are provided in high-density polyehtylene (HDPE) bottles with polypropylene (PP) closure and desiccant. The hard capsule itself is a carrier and is not for consumption.

2.2.2. Active substance

The chemical name of hydrocortisone is 11β, 17α, 21- trihydroxy-pregn-4-ene-3,20-dione corresponding to the molecular formula $C_{21}H_{30}O_5$ and has a molecular weight of 362.5 and the following structure:

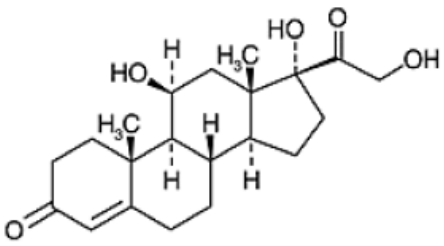

Figure 1. Structural formula of hydrocortisone.

The active substance is a white to almost white crystalline powder which is not hygroscopic.

Hydrocortisone is practically insoluble in water, sparingly soluble in acetone and in ethanol (96 per cent), slightly soluble in methylene chloride.

Hydrocortisone exhibits stereoisomerism due to the presence of four chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation.

Polymorphism has been observed for hydrocortisone. Three different polymorphic forms (Forms I, II and III) have been reported in the literature. Form I is the thermodynamically most stable form. It has been confirmed that the active substance is provided as a single polymorphic form 1, which is stable after more than 86 months in the stability program.

As there is a monograph of hydrocortisone in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for this active substance which has been provided within the current Marketing Authorisation Application.

Manufacture

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The substance is packed in a polyethylene (PE) bag or double polyethylene bags placed in a metal can or fibre drum as described in the CEP.

Specification

The active substance specification includes tests for: appearance (Ph. Eur.), identity (IR, HPLC), assay (UV), specific optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), related substances (Ph. Eur.), residual solvents (GC), chromium (ICP), particle size (electrical sensing zone method).

This specification is in line with the CEP, which in turn is consistent with the current version of the Ph. Eur. monograph for hydrocortisone no. 335, and the additional tests for residual solvents (methanol), residual catalyst (chromium) and particle size distribution described in the CEP.

The active substance particle size is tightly controlled by the specification. The specification limit has been justified based on the proposed manufacturing process for the finished product.

The polymorphic form of hydrocortisone is controlled in the specification of the active substance manufacturer by infra-red (IR) spectroscopy test form and additional periodic testing using X-Ray Diffraction

(XRD). Based on this and the stability of the polymorphic form, the absence of a test for polymorphic form by the finished product manufacturer is considered justified.

The non-compendial analytical methods were assessed by EDQM during the certification procedure and are covered by the CEP.

Batch analysis data for 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions at 25ºC / 60% RH (17 batches) or for up to 24 months under intermediate conditions 30ºC / 65% RH (2 batches) according to the ICH guidelines were provided. The active substance was packaged in two PE bags, twist-tied inside a fibre drum.

The following parameters were tested: assay (Ph.Eur.), loss on drying (Ph.Eur.) and related substances. An additional test for total impurities was implemented after initiation of the stability study.

All tested parameters were within the specifications at all time points and no trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. No significant changes in appearance, colour in solution and assay were observed. Impurities were at or below 0.10%, and all results were within the specification. Therefore it was concluded that hydrocortisone is photostable and no additional light protective measures for the active substance during storage or during manufacture of the finished product are required.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months at controlled room temperature in the proposed container with the storage recommendation “do not store above 30°C”.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as oral immediate release granules in capsules for opening containing 0.5 mg, 1.0 mg, 2.0 mg or 5.0 mg of hydrocortisone as active substance.

Other ingredients are:

Capsule contents: microcrystalline cellulose, hypromellose, magnesium stearate and ethyl cellulose

Capsule shell: hypromellose.

Printing ink:

0.5 mg capsules: shellac, propylene glycol, concentrated ammonia solution, potassium hydroxide, red iron oxide (E172).

1 mg capsules: shellac, propylene glycol, concentrated ammonia solution, indigotine (E132).

2 mg capsules: shellac, propylene glycol, concentrated ammonia solution, indigotine (E132), yellow iron oxide (E172), titanium dioxide (E171).

5 mg capsules: shellac, propylene glycol, concentrated ammonia solution, potassium hydroxide, titanium dioxide (E171), black iron oxide (E172).

This pharmaceutical form has been specifically developed for use in children aged less than 6 years as replacement therapy of adrenal insufficiency. It may also be used by older children unwilling or unable to swallow the traditional tablet formulation.

The granules are placed into hard transparent capsules (size 00el) which are packaged in HDPE bottles, closed with a PP child-resistant, tamper-evident closure with 2 g integrated desiccant, as described in section 6.5 of the SmPC.

The qualitative and quantitative composition of the granules is the same for all strengths but the hard capsules are filled at different fill weights to achieve the required dose. The coloured imprint on the capsule, which is different for each strength, differentiates the strengths. The imprints are:

"INF-0.5" (in red ink) for the 0.5 mg strength

"INF-1.0" (in blue ink) for the 1.0 mg strength

"INF-2.0" (in green ink) for the 2.0 mg strength

"INF-5.0" (in grey ink) for the 5.0 mg strength

The hard capsule itself is used as a carrier and is not intended to be consumed.

As indicated previously, the active substance, hydrocortisone micronised is covered by a CEP. The active substance is provided as a single polymorphic form and its particle size is tightly controlled by the active substance specification.

As the proposed product is intended to be used for very young children, the initial selection of the potential excipients for use within the proposed finished product was based upon two key factors: the excipient should be "Generally Recognized As Safe" (GRAS) approved, and the excipient will have been previously used within a licensed paediatric medicinal product. All excipients selected are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. The microcrystalline cellulose spheres and the hard capsules conform to the suppliers specifications presented. Microcrystalline cellulose used in the manufacture of the microcrystalline cellulose spheres and hypromellose used to manufacture the hard capsules comply with the current Ph. Eur. monographs. Additional functionality related tests for the cellulose spheres (particle size distribution, loss on drying, friability and swelling index) have been described and validated. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The compatibility of hydrocortisone and the proposed excipients was confirmed in a formulation development study. Furthermore, the overall compatibility between the active substance and the excipients, and between the finished product and the packaging materials has been demonstrated by the stability testing program carried out on the finished product.

The aim of the pharmaceutical development was to develop an age-appropriate formulation of hydrocortisone for the treatment of children. The unmet medical need identified by the applicant included a lack of

appropriate dosage strength. The smallest current tablet strength of 10mg has to be crushed and then split into smaller doses, resulting in inaccurate dosing; the bitter taste of hydrocortisone in the crushed tablet; the absence of safety, efficacy or pharmacokinetic (PK) data in subjects aged below 18 years; and serious potential consequences of under- or over-dosing children with the currently available preparations.

As a result, the quality target product profile (QTPP) was to develop an oral immediate release formulation which would provide taste masking, is suitable for paediatric patients, provides an accurate dosing at low paediatric dose strengths and can be mixed and administered with suitable fluids and foods. In order to achieve the desired product characteristics, a multiparticulate granule was selected. The selected formulation and pharmaceutical form has been adequately justified by the applicant providing reference to relevant regulatory guidance, scientific literature, other marketed products and previous consultation as part of the Paediatric Investigation Plan. The swallowability of the granules, the potential risk of choking, and the possibility that some of the granules are retained in the mouth and will be absorbed buccally has also been discussed. No difference in bioavailability is claimed being expected since hydrocortisone has a mean bioavailability of 96% by the oral route.

The choice of the core microspheres, drug layering, seal coat and taste masking coat were investigated as part of the formulation development.

Different spheres were evaluated for their suitability as the carrier for the Alkindi formulation. The selection of the microcrystalline spheres was justified For drug layering, different binders were discussed. The hypromellose binder was shown to provide greater efficiency for drug layering. Relevant information was provided to justify the proposed seal coat. Different taste masking systems were evaluated. the final composition of the system was selected.

In order to deliver the granules to the patient a carrier capable of containing an accurate dose for all dose strengths and easy to be handled by the patient caregiver was pursued. A hypromellose (vegetable-derived) size “00el” hard capsule carrier was preferred. The hard capsule size of ‘00el’ was chosen for ease of handling and opening. A transparent shell was chosen, to visually certify the capsule is empty. There are no toxic components in the capsules and they comply with EP, USP and JP standards.

The Alkindi granules in capsules for opening are packaged in HDPE bottles sealed with a PP lid with integrated desiccant. The primary packaging protects the granules in capsules from moisture.

The composition of the product used in the clinical trials is identical to the one proposed for commercialisation.

Bioequivalence of the Alkindi granules to the reference hydrocortisone tablet product (hydrocortisone 10 mg tablets Auden Mckenzie)has been demonstrated in clinical studies Comparative *in vitro* dissolution profiles for the reference product from the European market and the biobatch (Alkindi 5 mg), at pH 1.2, 4.5 and 6.8, using the QC method have been presented. The results indicate that both products meet the dissolution criteria as defined for an immediate release product (Q=75% at 45 minutes). Bioequivalence between both products has been demonstratedData has been provided to demonstrate that even though biobatch and industrial batch are vastly different in size, their dissolution profiles and manufacturing process can be considered as comparable. In fact, in order to demonstrate that the Alkindi investigational medicinal product used in the clinical study,, is representative of the product to be marketed,a larger scale, a comparative *in vitro* dissolution profile testing study was undertaken. The dissolution profiles produced in each media demonstrate that the batches of Alkindi granules produced at the different scales have a similar dissolution performance (f2>50) in all three media tested, namely pH 1.2),4.5 and 6.8. It was also confirmed that the composition and manufacturing process parameters are comparable.

Clinical study Infacort 003 was performed with industrial batches of the four strengths.

The active substance, hydrocortisone, is a BCS (Biopharmaceutics Classification System) class 1 molecule, being highly soluble and highly permeable. Its bioavailability from the gastrointestinal tract has been determined to be 96% for an oral 20 mg dose (Derendorf, 1991) and its solubility is not significantly affected by pH. Hydrocortisone has been shown to be soluble across the physiological pH range (pH 1 to 7). There is no significant difference in solubility across this pH which would present a risk to the physicochemical performance of the finished product.

The influence of the particle size distribution of the active substance and finished product granules on dissolution performance was considered when developing Alkindi granules. As mentioned above, particle size distribution is controlled in the active substance specification. The method of manufacture of the granules is a standard fluidised bed spray-layering technique. The particle size of the granule is adequately controlled.

Dissolution development studies were conducted to ensure that the dissolution conditions were optimised to be discriminatory to detect changes in the product and could, therefore, control batch to batch consistency. The method was developed to detect changes in the granule formulation which may impact hydrocortisone release *in vivo*. To verify the discriminatory nature of the QC dissolution test, batches of the finished product manufactured at different were evaluated during the development programme.

The granule taste mask coating has been demonstrated to be effective in the oral cavity; following administration in clinical studies Infacort 001 and Infacort 002 the majority of subjects confirmed Alkindi granules were acceptable and palatable, and in clinical study Infacort 003 the majority of paediatric patients also confirmed the palatability of Alkindi granules. To verify the *in situ* integrity and correct application of the taste-masking layer, for the purposes of supporting the dosing posology for the product to paediatric patients, and batch to batch consistency, the applicant was requested to add an early time point to the proposed dissolution test or to develop an alternative test to control the functionality of the taste masking layer. The applicant conducted dissolution studies in a separate biorelevant model. Based on this investigation an alternative *in vitro* dissolution method to control the functionality of the taste masking layer was introduced as an in-process control (IPC) with the results being part of the release specification. This test was demonstrated to be discriminatory against the amount of taste mask coating. This test is used to support the applicant's claim that Alkindi granules maintain their taste masking integrity. The proposed limit is clinically acceptable since the method of administration described in the SmPC indicates that that dosing with dry granules should be followed immediately by a drink to wash the product down; or, where sprinkled onto a spoonful of soft food, this should be given within 5 minutes and not stored for future use, as explained above.

In order to manufacture the multiparticulate granules, a fluidised bed bottom spray coating (Wurster coating) process was chosen for each of the layering steps. The rationale for developing this process was justified. The manufacturing process development data presented demonstrate the consistent quality of the granules following scaling-up from the development batch size to the industrial batch size.

The proposed granules have low bioburden potential due to the use of the organic solvent in the final taste mask coating step of the multiparticulate granules manufacturing process. Microbial limit acceptance according to the Ph Eur/USP harmonised method for the microbiological examination of non-sterile products has been established.

As indicated above, Alkindi granules are designed for oral administration into the mouth and washed down immediately with fluids, or mixed with a spoonful of soft-food and washed down with fluids immediately following administration. Compatibility of the Alkindi granules with administration fluids (including breast milk, whole milk, formula (artificial) milk and water) and soft-food matrices commonly used for co-

administration of medicines (yoghurt and apple sauce) was demonstrated through *in vitro* dissolution and compatibility studies. The results obtained confirm the compatibility of Alkindi with commonly used administration fluids like water, breast milk, formula milk and whole milk and support the proposed administration instructions for use included in section 4.2 of the SmPC. In most of the simulated dosing scenarios *in vitro* dissolution was rapid and complete with no drug precipitation observed over the experiment duration. These results indicate that it is likely that *in vivo* dissolution and bioavailability of hydrocortisone from Alkindi granules will not be adversely affected by the composition of the co-administered dosing fluids or co-administered soft-foods studied, particularly when the method of administration instructions in the SmPC are followed and the granules mixed in soft-food are washed down immediately with fluid after oral administration.

The potential administration of the granules through nasogastric tubes was also investigated. The results obtained indicate that the granules stick to the tubes (6 Fr and 8 Fr) and are not expelled following flushing. Therefore, it was concluded that the smaller tubes do not allow proper administration of Alkindi. This is reflected in the SmPC section 4.3 and leaflet section 2.

The containers used for bulk hydrocortisone immediate release granules and bulk capsules have been described They comply with the relevant Ph. Eur. Monograph.

The primary packaging of the finished product consists of an opaque HDPE bottle containing 50 capsules. Bottles are closed with a child-resistant, tamper-evident PP screw cap with 2 g integrated desiccant. The sealed bottles are placed into a secondary cardboard carton. All packaging materials are commonly used for packaging of solid oral dosage forms and conform to EU Directives for pharmaceutical packaging materials. The resins in the bottles meet the Ph. Eur. monograph 3.1.3 (Polyolefines). The HDPE in the bottles are in compliance with EU regulation 10/2011 on plastic materials and articles intended to come into contact with food. The closure is a round, polypropylene, child-resistant, tamper-evident screw cap with integrated desiccant. The resins in the closures meet the EP Monographs 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) and 3.1.3 (Polyolefines). The closure is in compliance with EU regulation 10/2011 and is certified child resistant according to ISO8317 (2003). The desiccant complies with Regulation (EC) 1935/2004 and EU regulation 10/2011.

Manufacture of the product and process controls

The manufacturing process consists of three coating steps: preparation of hydrocortisone coated granules, seal coating and taste mask coating of the granules by fluid bed spray-layering, followed by capsule filling at different fill weights to produce the different dose strengths and packaging. The process is considered to be a standard manufacturing process. The hold time for the granules has been validated during process validation.

The IPCs are adequate for this type of manufacturing process.

The finished product manufacturing process has been validated through the manufacture of one process validation campaign consisting of three consecutive commercial scale finished product batches, including all capsule strengths, in accordance to a pre-approved protocol. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (UV, HPLC), assay (HPLC), uniformity of dosage units by content uniformity (Ph. Eur.), dissolution (both release characteristics and taste mask functionality), residual solvents (GC), impurities (HPLC), microbiology (TAMC, TYMC, *E.coli*- Ph. Eur.).

During the review, there was a major objection by the CHMP and the applicant was requested to revise the dissolution specification. This resulted in the development of an alternative in vitro dissolution method to verify the *in situ* integrity and correct application of the taste-masking layer to support the dosing posology to paediatric patients and batch to batch consistency. The applicant was also requested to demonstrate that the proposed dissolution limit and acceptance criteria had been set with reference to the dissolution results obtained with the batches used in the bioequivalence studies.

The absence for a limit for water content/loss on drying in the finished product specification has been justified by the applicant.

The specifications for Alkindi have been chosen in line with the requirements of ICH Q6A. Due to the concentration of the active within the dosage form, uniformity of dosage units is confirmed by content uniformity testing. The limit has been set in line with the Ph. Eur. test. The related substance specification is based on the hydrocortisone Ph. Eur. monograph and is set in accordance with ICH Impurities Guideline Q3B(R2). The residual solvent specification has been set against ICH Q3C (R4).

In line with ICHQ3D an assessment of the potential for the presence of elemental impurities within the finished product has been undertaken. Based on the findings of the risk assessment, the applicant concluded that the controls in place for the active substance and excipients are appropriate and justified to control the potential elemental impurity content in the finished product.

The impurity profile for hydrocortisone complies with the Ph. Eur. monograph for hydrocortisone.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The stability indicating nature of the HPLC method for related substances has been demonstrated through stress studies. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability studies on hydrocortisone immediate release granules filled in capsules have been conducted in accordance with ICH Q1A and Q1B.

Stability data of three registration batches of Alkindi 0.5 mg and 5.0 mg batches stored under long term conditions for up to 24 months at 30 ºC/75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The use of the 30°C/75% RH long term storage condition, instead of 30°C/65% RH, has been justified support registration of the product in other global territories, including those defined as Climatic Zone IVb.

A bracketing approach using the highest and lowest available dose strengths for the long term stability studies has been followed and is considered acceptable

The batches of Alkindi were identical to those proposed for marketing and were packed in 100 ml HDPE bottles sealed with PP screw cap with desiccant containing 25 or 40 capsule fill count. The stability data for the 40-count in 100 ml HDPE bottles is claimed to be fully representative of the stability of capsules packed as proposed for marketing since the material composition is the same and the ratio of fill count to bottle volume and headspace is maintained constant.

Supportive stability studies on two development batches of Alkindi 0.5 mg and 5.0 mg stored at 25ºC/60%RH for up to 24 months and 40ºC/75%RH for up to 6 months have also been presented.

Stability batches were tested for appearance, assay, purity, dissolution and microbiology (annually), according to the limits and methods described above.

Results of all the stability studies conducted showed good stability of the proposed product over time under the conditions studied. Under long term study conditions no significant changes and no trend were observed in most of the parameters controlled over the tested period of 24 months. Under accelerated test conditions, a slight increase of some impurities was observed but all results remained within the proposed specification On the basis of the note for guidance on evaluation of stability data the applicant proposed a shelf-life of 30 month. In line with the requirements of the Ph.Eur. general monograph for Capsules, the special storage condition “Do not store above 30°C” is applied.

A photostability study has also been conducted on one commercial scale batch of Alkindi 5.0 mg. Samples were exposed to light without the primary packaging or packaged in HDPE bottles. Photostability batches were tested for appearance, assay and purity. The product showed signs of degradation after exposure to light without the protection of the HDPE container, and some impurity levels were out of specification. Therefore, it was concluded that the finished product is photosensitive and should be stored in the original bottle in order to protect from light.

Stability studies to support bulk granule storage prior to encapsulation were also conducted. The data after storage for the proposed holding period at the warehouse storage conditions were all within the specification and no trends were observed. The stability results from this bulk hold study support the proposed storage of the granules in bulk prior to encapsulation. In addition, stability studies were conducted on one commercial scale batch of Alkindi 0.5 mg and 5.0 mg to support bulk capsule storage and transport prior to primary bottle packaging. The data after storage for the proposed holding period showed that all results are within specification and no trends in data were observed. The stability results from each study support the proposed storage holding period and storage conditions for the bulk capsules prior to primary packaging.

In-use shelf life stability testing of hydrocortisone immediate release granules filled in capsules packaged in the packaging material proposed for marketing and stored at 25ºC/60%RH was also studied. The study was conducted in accordance with EMA Guidance on in-use stability testing of human medicinal products stored in multidose containers (CPMP/QWP/2934/99). Two batches of 0.5 mg dose strength capsules stored in 50-count HDPE bottles/PP screw cap with desiccant were tested. Samples were stored at 25°C/60%RH, the bottles were opened daily and capsules removed at defined intervals to simulate routine use. Capsules were tested after 0, 7, 14, 28, 42 and 60 days for appearance and after 0, 28 and 60 days for appearance, assay, purity, dissolution and microbiology. The data after storage for 28 and 60 days showed that all results are within specification and no trends in data were observed. The in-use stability data demonstrates the quality of the product remains constant over the proposed in-use shelf-life of 60 days once the HDPE bottle has been opened.

Satisfactory data has been generated to support in-use stability, photostability and bulk storage of granules and capsules.

Based on available stability data, the proposed shelf-life of 30 months and storage conditions “do not store above 30°C” and “store in the original bottle in order to protect from light”, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The information on the active substance micronized hydrocortisone refers to the valid CEP and therefore raised no comment. The stability data presented by the applicant supports the 24 month retest period in the proposed container with the storage recommendation “do not store above 30°C”.

Alkindi granules in capsules for opening constitutes new paediatric-specific presentation of the established active pharmaceutical ingredient, hydrocortisone to improve its dosing and overcome the bitter taste of the crushed tablets. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Bioequivalence with the reference product has been demonstrated. Although the bioequivalence studies were performed with a development batch of 2 kg an appropriate justification to demonstrate that this batch is representative for the industrial batch size has been presented. Two dissolution methods were developed, one to control the taste mask coating and the second one to control hydrocortisone release. The dissolution method for hydrocortisone release is discriminant and the limits were set with reference to the dissolution results obtained with the batches used in the bioequivalence studies.

The manufacturing process description is provided with sufficient details, including in-process controls and possible holding steps. The process was suitably validated. The tests proposed in the specifications are appropriate and a summary of the risk assessment of the elemental impurities is included, in line with ICH Q3D.

Stability studies were conducted in accordance with the ICH recommendations, including long term (up to 24 months) and accelerated conditions, in-use study, photostability and bulk stability. These justify the proposed shelf life and storage recommendations.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Alkindi consists of uniform multiparticulates, which have an inert core, a hydrocortisone drug layer, a hydroxypropylmethyl cellulose seal coating layer and an outer ethyl cellulose/hydroxypropylmethyl cellulose taste masking layer All of the pharmaceutical excipients are well known and commonly used in the pharmaceutical industry and fulfil the requirements of the European Pharmacopoeia (Ph. Eur.).

Dosage must be individualised according to the response of the individual patient.

Evaluation of the PK, PD and safety of Alkindi has been conducted through clinical studies.

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. Pharmacodynamic, pharmacokinetic and toxicological properties of hydrocortisone are well known. As hydrocortisone is a widely used, well-known active substance, the applicant has not provided additional studies and further studies were not required. Overview based on literature review was, thus, appropriate.

The non-clinical aspects of the SmPC were in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies were required.

2.3.2. Pharmacology

No non-clinical pharmacology studies have been performed with Alkindi granules, which is acceptable. Hydrocortisone is a synthetic glucocorticoid and the pharmaceutical form of the major endogenous glucocorticoid in man, cortisol. Thus, the pharmacological effects of hydrocortisone in man are identical to cortisol e.g. metabolic actions on carbohydrates, proteins and fat as well as anti-inflammatory and immunosuppressive actions. Moreover, the pharmacological properties of hydrocortisone, both primary and secondary are well-known given the extensive clinical experience with hydrocortisone in the proposed indication.

No drug interaction studies or GLP safety pharmacology studies have been performed with Alkindi, which is acceptable given the long experience of use of hydrocortisone in man, including at immunosuppressant and anti-inflammatory doses many times higher than those which will be needed for replacement therapy in adrenal insufficiency where the peak systemic levels obtained with the treatment will be within the normal levels of cortisol in healthy humans.

2.3.3. Pharmacokinetics

No non-clinical pharmacokinetic studies were performed using Hydrocortisone granules and there is only limited information available on the absorption, distribution, metabolism and excretion (ADME) of hydrocortisone in animals in the published literature.

Hydrocortisone presents low solubility but high permeability through the intestinal membrane with inter-individual variability. The distribution phase is very rapid, with a terminal half-life of 1.28±1.6 hours. In pregnant mice transfer to the embryos has been described. Hydrocortisone undergoes hepatic metabolic clearance in rats and dogs. In rats, it is excreted mainly via the faeces and also in the urine. Other drugs may affect cortisol clearance by inducing or inhibiting the various enzymes involved in the metabolism of cortisol.

No study assessing the excretion of hydrocortisone in human milk has been identified. Endogenous cortisol is, however, excreted in breast milk at a stable rate throughout the lactation period, so it is reasonable to assume that hydrocortisone can also be present in breast milk.

For the purpose of this marketing authorisation application and in line with the agreed paediatric investigation plan, the pharmacokinetics of Alkindi have been investigated in clinical studies.

2.3.4. Toxicology

No standard repeat-dose toxicity studies or information regarding toxicokinetics or interspecies comparisons has been identified in the literature. In single dose toxicity studies in rats, adverse effects included infections possibly related to the immunosuppressive properties of hydrocortisone, reduced adrenal weights, liver damage, lung consolidation and gastrointestinal changes. Repeated-dose toxicity studies in rats and rabbits reported the liver as target organ. Hepatotoxicity is a known effect of high dose glucocorticosteroids.

With respect to genotoxicity, older studies in mice indicate a clastogenic potential of hydrocortisone. However, a more recent standard battery of GLP compliant *in vitro* and *in vivo* genotoxicity studies do not indicate a genotoxic potential of hydrocortisone.

Carcinogenicity studies have not been identified. However, an abstract of a life span study in rats reports that no evidence of a carcinogenic potential was found for hydrocortisone.

The available reproductive toxicity data demonstrate that hydrocortisone and other glucocorticoids in high doses have teratogenic and embryotoxic potential in various animal species. Adverse effects on offspring include cleft palate, sex organ anomalies, polycystic kidney disease, reduced lung and body weight. In a prenatal study in pregnant rats, indications of hormonal disturbances in the adult offspring were seen.

Juvenile animals studies have not been conducted to support this paediatric use marketing authorisation, which is considered acceptable in view of the clinical experience in children and which is also in line with the agreed PIP where no further non-clinical studies were requested to support the paediatric development of hydrocortisone.

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Alkindi manufactured by DIURNAL LTD is considered unlikely to result in any significant increase in the combined sales volumes for all hydrocortisone containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

As the current product is an alternative formulation for hydrocortisone preparations that are currently authorised, a shift towards this formulation is anticipated, without impacting overall environmental exposure. Furthermore, the use of precise dose units as offered by Alkindi may reduce environmental exposure compared to existing hydrocortisone products used in this formulation, as there is the potential to prevent

wastage from leftover portions after currently available tablets are cut up.

2.3.6. Discussion on non-clinical aspects

There is limited information in the published literature on the (safety) pharmacology, pharmacokinetics and toxicological properties of hydrocortisone in animal studies. Hydrocortisone is the pharmaceutical form of the endogenous glucocorticoid, cortisol. It has been used in clinical settings for decades and the overall knowledge of its pharmaco-toxicological properties in humans is extensive. In addition, Alkindi is indicated for treatment of adrenal insufficiency and the peak systemic levels obtained are within the normal levels of cortisol in healthy humans.

2.3.7. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Alkindi granules in capsules for opening and justifications that the different formulation of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Alkindi granules in capsules for opening containing hydrocortisone. To support the marketing authorisation application the applicant conducted two bioequivalence studies Infacort 001 and Infacort 002: both single centre, single dose, open-label, randomised with cross-over studies design under fasting conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment *EMA Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/ Corr* ** is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

Two bioequivalence studies Infacort 001 and Infacort 002 using 10 and 20 mg dose levels administered as 2x5 mg and 4x5 mg granules have been conducted while the procedure concerns the strengths 0.5 mg, 1.0 mg, 2.0 mg and 5 mg. The following general biowaiver criteria described in the *EMA Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/ Corr* ** were considered fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process.

b) the qualitative composition of the different strengths is the same;

c) the composition of the strengths are quantitatively proportional because the same immediate release granules are filled at different fill weights in the hard capsule to achieve the required dose;

d) the dissolution profiles of the 0.5 mg, 1 mg and 2 mg appears to be visually rather similar to the biobatch 5 mg used in the bioequivalence studies.

Regarding the linearity of the pharmacokinetics of the active substance, a less than proportional to dose-exposure relationship with increasing doses of Alkindi over the dose range from 0.5mg to 10mg has been shown, with a difference in dose-adjusted mean AUCs of more than 25% (study Infacort 001 – see the table below). The mechanism behind the non-linearity has been attributed by the Applicant to saturation of the protein-binding at higher doses. The absorption that was almost complete at the high dose of 20 mg (absolute bioavailability of 87% - study Infacort 002) supports that saturation of the absorption cannot be the main reason for the non-linearity.

In case of a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established at the highest and at the lowest strength (or a strength in the linear range) (*EMA Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/ Corr* **). However, the lowest available strength of an immediate release hydrocortisone product for which a marketing authorisation has been granted in the Union is the 10 mg strength used in the bioequivalence study Infacort 001 in healthy adult volunteers. A bioequivalence study at the lowest strength of Alkindi®, 0.5 mg, is thus not feasible. The applied product is appropriate for paediatric dosing and the granules are the same in all strengths of the product. Also, the theoretical uncertainty of bioequivalence between the lower strengths of Alkindi and the corresponding dose of the reference product is likely minor in relation to the overall uncertainty in the off-label crushing and dividing of the reference product, which is the common practice used in the clinical settings today. Even if some uncertainties remained on the determination of the C_{max} in the study Infacort 001 (see below), taking into account the results from the bioequivalence study Infacort 002 conducted with the 20 mg strength and from the clinical studies Infacort 003 and 004, because the development of this new formulation with the same granules for all capsule strengths respond to an unmet medical need in paediatric patients and since the dose is individually titrated based on the clinical response, this issue was not further pursued.

Table 1: Summary of statistical analysis of dose proportionality of Alkindi® using baseline adjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression (Infacort 001)

	Infacort® 0.5mg (n=15)	Infacort® 2mg (n=15)	Infacort® 5mg (n=15)	Infacort® 10mg (n=14)	Slope	95% C.I. for Slope
Dose Proportionality (Geometric LSmean)						
C_{max} (nmol/L)	72.15	225.74	399.57	581.63	0.702	0.658 - 0.746
AUC_{0-t} (hr*nmol/L)	119.76	438.28	897.95	1567.39	0.858	0.833 - 0.883
AUC_{0-inf} (hr*nmol/L)	121.36	441.64	901.17	1573.50	0.855	0.829 - 0.881
Dose Independence (LSmean)						
t½ (hr)	0.98	1.26	1.15	1.33	0.026	0.000 – 0.052
CL/F (L/hr)	11.66	12.71	15.49	17.73	0.649	0.541 – 0.757

Results for C_{max} and AUCs obtained using an ANOVA on log-transformed data with a fixed effect of log-transformed dose and a random effect of subject. Results for t½ and CL/F obtained using same method on non-transformed data.
Subject 11 was not included in the dose proportionality analysis since they only had one dose level with suppressed pre-dose cortisol (Infacort 2 mg).
ANOVA = analysis of variance.

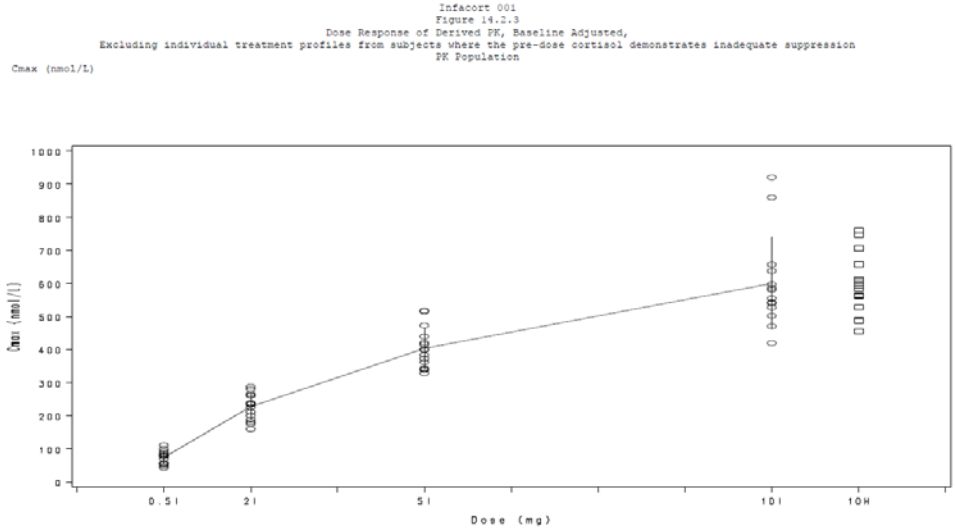

Figure 1: C_{max} dose response, baseline adjusted, excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrates inadequate suppression

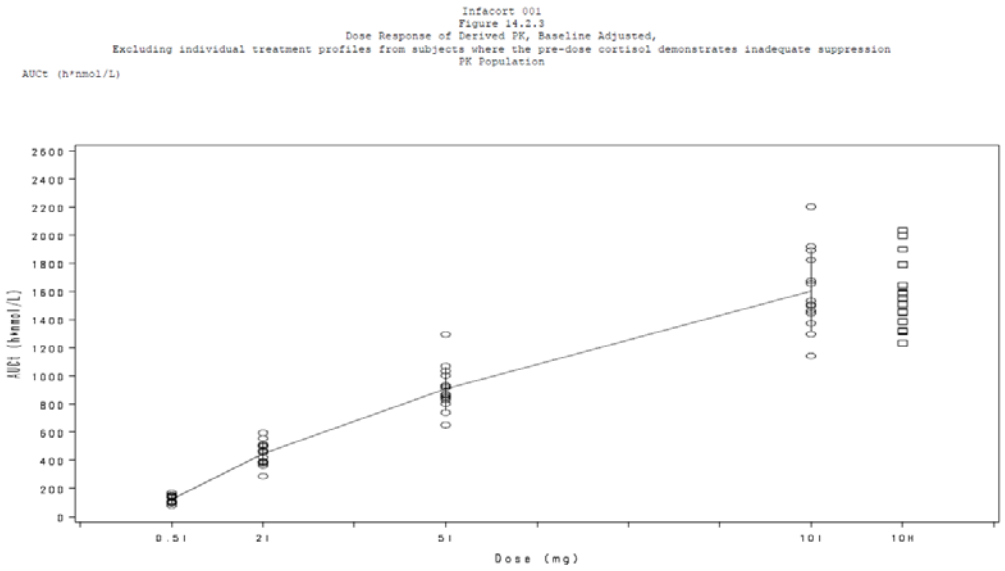

Figure 2: AUC_{0-t} dose response, baseline adjusted, excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrates inadequate suppression

Clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies.

Table 1. Tabular overview of clinical studies

Table 2: Summary of the clinical studies contributing to the PK of Alkindi® in healthy volunteers

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Dosage; Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE, PK	Infacort 001	Module 5.3.1.2	Primary: To compare the PK of Infacort vs. IRHC at a single dose of 10mg and to determine the dose proportionality for Infacort at doses of 0.5mg, 2mg, 5mg and 10mg	Single centre, open-label, randomised, crossover study IRHC tablet	Infacort oral granules at doses of 0.5mg, 2mg, 5mg and 10mg given as a single dose. 10mg IRHC	16	Healthy subjects	Single dose	Complete; Full
BE, PK	Infacort 002	Module 5.3.1.2	Primary: To determine the absolute and comparative bioavailability of cortisol from Infacort granules and IRHC tablets using i.v. hydrocortisone as the reference injection	Single centre, open-label, partially randomised, crossover study IRHC tablet and i.v. hydrocortisone	Infacort 20mg oral granules, IRHC 20mg oral tablet, or hydrocortisone 100/mL solution for i.v. injection	14	Healthy subjects	Single dose	Complete; Full

In addition to the studies in healthy volunteers, additional samples were taken for population PK analysis in the oldest age group of patients receiving a single dose of Alkindi® included in the phase III study Infacort 003 (secondary objective). The Applicant has planned to analyse and present these data separately in the first quarter of 2018. As a prerequisite, the data analysis plan should be submitted as soon as possible**.**

Table 3: Summary of the phase III study contributing to the PK behaviour of Alkindi in patients

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Dosage; Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and efficacy	Infacort 003	Module 5.3.5.2	Primary: To demonstrate significant absorption of hydrocortisone from the Infacort preparation	Single centre, open-label, single dose study No control	Infacort given orally as a single dose, with the dose being equivalent to the previous day's morning dose	24	Subjects <6 years old with a diagnosis of AI and a clinical need for cortisol replacement therapy	Single dose	Complete; Full

2.4.2. Pharmacokinetics

Two bioequivalence studies Infacort 001 and Infacort 002 have been conducted **to compare the pharmacokinetics of the new formulation Alkindi 2X5mg and 4X5mg with Hydrocortisone immediate release tablets 10 mg and 20 mg, respectively** (see the tables below). The dose proportionality of Alkindi at doses of 0.5 mg, 2 mg, 5 mg and 10 mg was also investigated in the study Infacort 001 (see before). Another primary aim of the study Infacort 002 was to determine the absolute bioavailability of cortisol from Alkindi® granules and hydrocortisone tablets using intravenous hydrocortisone as the reference injection. Secondary objectives of the study Infacort 002 included building a model of hydrocortisone metabolism and evaluating relationship to metabolic parameters of hydrocortisone and Alkindi.

Table 4: Summary of study design (Infacort 001)

Screen (Days)	Treatment Period (s)*				Post Study (Days)
	N	IMP			
-14 to -1	16	Infacort®	0.5 mg	Multi-particulate granules from 1 (0.5 mg) capsule	3-7 days *(after final IMP)*
		Infacort®	2 mg	Multi-particulate granules from 1 (2 mg) capsule	
		Infacort®	5 mg	Multi-particulate granules from 1 (5 mg) capsule	
		Infacort®	10 mg	Multi-particulate granules from 2 (5mg) capsules	
		Hydrocortisone	10 mg	1 (10 mg) tablet	

* Each IMP was administered to each subject in a randomised crossover manner over 5 Treatment Periods (1 treatment/period). During each Treatment Period, each subject was admitted to the Unit in the afternoon of Day 1 and remained in the Unit until completion of all scheduled assessments on Day 2. Each subject received their scheduled IMP on the morning of Day 2 at ~ 07.00 hrs (fasted). Each subject also received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22.00 hrs on Day 1, and at approximately 06.00 hrs and 12.00 hrs on Day 2. All doses were administered with 200 mL water. There were at least 7 days (washout) between each dose of IMP. IMP = investigational medicinal product.

Table 5: Summary of study design (Infacort 002)

Screen (Days)	N	Study Period*	Treatment			Post Study (Days)
-14 to -1	14	1	No IMP: No Treatment		Endogenous cortisol measurement	3-7 days *(after final IMP)*
		2	NIMP: Dexamethasone	1 mg	2 (500 µg) tablets	
		3/4	IMP: Oral Infacort®	20 mg	Multi-particulate granules; contents of 4 capsules each containing 5 mg of granules);	
			IMP: Hydrocortisone tablet	20 mg	1 (20 mg) tablets	
		5	IMP: i.v. Hydrocortisone	20 mg	0.2 mL (100 mg/mL) solution for injection	

* No IMP (no treatment, dexamethasone, oral Infacort®, hydrocortisone tablets and i.v. hydrocortisone were administered to each subject over 5 Study Periods (1/period). During each Study Period, each subject was admitted to the Unit on Day 1 (morning of Study Period 1 and afternoon of Study Periods 2-5) and remained in the Unit until completion of all scheduled assessments on Day 2. *Study Period 1:* no IMP (no treatment) was administered and endogenous cortisol production was measured. Given the diurnal variation in cortisol production subjects prepared for bedtime from 22:00 with lights out from 23:00 to 06:00. *Study Periods 2 - 5:* each subject received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22:00 on Day 1, and at approximately 06:00 and 12:00 on Day 2. Each subject also received oral Infacort® and hydrocortisone tablets (randomised over Study Periods 3/4) and i.v. hydrocortisone (Study Period 5) on the morning of Day 2 at ~ 07:00 (fasted). All oral doses were administered with 200 mL water. As cortisol is important in metabolism, and specifically insulin sensitivity, during each study period a standard mixed meal was served on Day 1 at 13:00 (Study Period 1 only) and 19:00 and on Day 2 at 08:00 and 13:00. There were at least 7 days (washout) between Day 1 of each study period. i.v. = intra venous, IMP = investigational medicinal product. NIMP = non investigational medicinal product. **Data Source:** Appendix 16.1.1, Appendix 16.2.3, Listing 16.2.3.1

The two bioequivalence studies were single centre, single dose, open-label, randomised, cross-over studies. The sample size was appropriate. However, **for the study Infacort 001, the infrequent sampling around t_{max} casted doubts on the measurement of true C_{max} since about half of the volunteers in each treatment group presented the C_{max} being the first point of the concentration time curve (0.5 h)** for the 10 mg Alkindi and 10 mg test reference tablet and even more subjects for Alkindi 0.5 mg, 2 mg, 5 mg. The reasons for this "shift" in t_{max} couldn't be identified. The reassessment of the bioequivalence after the exclusion of these subjects was not possible as it would lead to a number of evaluable subjects of less than 12, the minimum number of subjects requested in the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr **)*. **The C_{max} could therefore not be reliably estimated in the study Infacort 001** and conclusions done for the bioequivalence between 2x5 mg Alkindi and Hydrocortisone 10 mg as well as the dose proportionality of the different strengths of Alkindi for this PK parameter could not be relied upon. However, **even if some uncertainties remained** on the determination of the Cmax in the study Infacort 001, taking into account (1) the results from the bioequivalence study Infacort 002 with t_{max} not being the first sampling point for any subjects (see also comment on statistical analysis below) and (2) the results from the clinical phase III studies Infacort 003 and 004, (3) because the development of this new formulation respond to an unmet medical need in paediatric patients and (4) a monitoring of the clinical response is recommended in the section 4.2 of the SPC, this issue was not further pursued.

Auden Mckenzie (Pharma Division) Limited 10 mg Hydrocortisone tablets PL 17507/0246 and 20 mg Hydrocortisone tablets PL 1707/00098 are the reference products used in the study Infacort 001 and Infacort 002, respectively. They have been granted market authorisation in the European Union on the basis of a complete dossier in accordance with Articles 8(3), of Directive 2001/83/EC. Both reference products (Hydrocortisone Auden Mckenzie 10 mg and 20 mg tablets) have the same indications and the same posology and method of administration in adults and children.

Details of the test and reference products used in the bioequivalence studies Infacort 001 and Infacort 002 are shown in the table below.

Table 6: Alkindi (test) and hydrocortisone reference products used in Infacort 001 and Infacort 002 clinical trials

ALKINDI	STRENGTH	PRESENTATION	ROUTE	BATCH NO.	EXPIRY DATE	SCALE	HYDROCORTISONE ASSAY RESULT	COUNTRY OF PURCHASE
Alkindi	5 mg	Granules*	Oral	0322/2013	10/2013**	2 kg	4.84 mg (97%)	-
REFERENCE								
Hydrocortisone Auden Mckenzie	10 mg	Tablet	Oral	12E22/A	05/2015	Comm.	10.06 mg (100.6%)	UK
Hydrocortisone Auden Mckenzie	20 mg	Tablet	Oral	12K28/G2	11/2015	Comm.	20.0 mg (100.0%)	UK

*multi-particulate granules are stored within in capsule

** further stability results covered the period of the study Infacort 002 conducted after the study Infacort 001

The comparative dissolution profiles with the biobatches of the test product Alkindi 20 mg and the reference product hydrocortisone 20 mg tablet used in the study Infacort 002 were lacking and a number of issues have been identified regarding the comparative dissolution profiles provided for the comparison between the 10 mg strength of the test and reference products used in the study Infacort 001. Because *in vivo* bioequivalence conclusions prevail, these issues raised were not pursued.

Alkindi used in the clinical study was manufactured at pilot scale while the product to be marketed is manufactured at a larger scale. However, appropriate justification has been presented to demonstrate that this batch is representative for the industrial batch size (see quality aspects before).

The CRO used in the bioequivalence studies, has been routinely inspected by the MHRA.

The studies Infacort 001 and Infacort 002 were conducted under **close to fasting conditions** (a meal has been given one hour after drug administration, while the EMA guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr** required that no food allowed at least 4 hours post-dose). Because **no food effect related recommendation is available in the SmPC of the reference product** Hydrocortisone 10 mg Auden MacKenzie (PL 17507/0246 - study Infacort 001), the bioequivalence should **preferably be tested under fasting conditions** as this situation will be more sensitive to difference in pharmacokinetics. In the literature (Barbhaiya R.H. et al, Drug-Nutrient Interactions, 1982; vol.1, p.103-112), **a food effect have been reported** with a reduction in the peak plasma concentrations and an increase in the time required to attain peak plasma concentrations for the administration of 3 x 20 mg hydrocortisone tablets after an overnight fast and following a standard breakfast in 10 healthy adult volunteers. However, the impact on the peak drug level appears to be rather limited with **the peak drug level under fed conditions representing about 85% of the peak drug level observed under fasting conditions** and after administration with 250 ml of water (Cmax = 0.57 µg/ml and 0.48 µg/ml under fasting and fed conditions respectively). **The data**

gathered up to now on efficacy and safety in the phase III clinical studies Infacort 004 conducted under real life conditions are reassuring. The Applicant has reported that the interim data from the long-term follow-up study do not suggest any gastrointestinal concerns in practice with this replacement dosage. Finally, **a monitoring of the clinical response is recommended in the section 4.2 of the SmPC**.

Different methods are proposed in the SmPC by the Applicant for the administration of Alkindi®: **administration of dry granules with a drink (water, milk, breast-milk, or formula milk) or sprinkled into soft foods, recommendation to dose promptly and then to give a drink (water, milk, breast-milk, or formula milk).** The volunteers and the majority of the patients included in phase I and III studies were administered Alkindi followed by water. Only two patients were described to receive Alkindi sprinkled into fruit mousse and 1 patient with (breast) milk. *In vivo* data available for these two last methods of administration are therefore limited. The **different methods proposed are however adapted to paediatric patients and can help to promote the medication compliance**. Regarding co-administration with meals, the impact of food will be probably rather limited. **Efficacy/safety data from study Infacort 004 collected in patients under real-life conditions are reassuring**. In addition, *in vitro* dissolution results in the presence of milk or soft food indicate that the presence of milk or soft food has no significant impact on the dissolution profiles: they are very similar to the profiles obtained in the absence of food, i.e. release is complete and rapid. **In a context of close clinical monitoring** allowing the adaptation of the dose administered according to the response of the individual patient, **the methods of administration described in the SmPC were endorsed**. Regarding the administration with soft food, the Applicant has reflected the results of the *in vitro* dissolution study in Section 5.2 of the SmPC.

The use of healthy adult male volunteers was considered appropriate for initial investigation of PK. This population was endorsed in the PIP. Another clinical study **Infacort 003** (efficacy study) has been conducted to evaluate whether Alkindi® provide adequate serum cortisol levels in paediatric patients (see below). Endogenous secretion of the hormone in healthy adult volunteers has been suppressed by dexamethasone pre-treatment.

The calculation of the PK parameters was performed using a baseline correction. In the study Infacort 002, a range of total serum cortisol concentrations from 7.67 to 40.94 nmol/L was found when the volunteers received only dexamethasone to suppress endogenous cortisol production and supports the use of a baseline correction. Two different pre-specified methods have been used for baseline correction for the calculation of the pharmacokinetic parameters for the clinical studies Infacort 001 and Infacort 002. For the study Infacort 001, the mean of the three pre-dose concentrations was subtracted from all post-dose concentrations for each period for each subject. It is one of the two methods for baseline correction proposed in *the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**)* when the substance being studied is endogenous: subtraction of the mean of individual endogenous pre-dose concentrations. The literature describes that in this case, the baseline level is usually taken as the mean of three or so levels in the 24 h prior to dosing (Dissanayake S. et al, BJCP, 2010, vol.69, p.238-244). The study Infacort 002 did not apply these recommendations. Indeed, all total serum cortisol concentrations were adjusted by subtracting only <u>one</u> pre-dose time point (the - 10 min sample) for each study period. Because the objectives of the study Infacort 002 were wider than the assessment of the bioavailability, the Applicant has chosen to reduce the number time points in order to keep the amount of blood taken for each period to a reasonable amount, including the number of pre-dose time points. The Applicant has however shown that the suppressed cortisol values in subjects were very stable when cortisol was suppressed with dexamethasone and can be considered as successfully suppressed as they were less than 50 nmol/l cortisol over the same period of 12 hours (study period 2 of the study Infacort 002) than the Alkindi® and hydrocortisone reference

tablet periods (study periods 3 and 4). Therefore it was concluded that **no real difference can be expected between the mean cortisol of three pre-dose values and the single cortisol value at pre-dose (-10 minutes).** It is considered acceptable taking into account that the Applicant has also reviewed the pre-dose cortisol concentration data for all subjects and all periods of the study Infacort 002.

Beside the use of a baseline correction, the Applicant has also realized the statistical analysis using ANOVA model including and excluding individual profiles from subjects where the pre-dose cortisol demonstrates inadequate suppression. No cut-off values for cortisol or adrenocorticotropic hormone (ACTH) suppression were specifically defined in the Infacort 001 and Infacort 002 studies. For the study Infacort 001, the Applicant has demonstrated the lack of impact of the subjects with inadequate cortisol suppression on the bioequivalence conclusion with the 90% interval confidence of the baseline adjusted PK parameters evaluated being within the interval acceptance range of 80.00-125.00% when the subjects are included or not included from the statistical analysis. For the study Infacort 002, when the subject where pre-dose cortisol demonstrated inadequate suppression was included in the statistical analysis, the 90% confidence interval around the geometric LS means ratio T/R was outside the upper acceptance limit for C_{max} (100.45-129.15 %). The underlying reason behind the high inadequate endogenous cortisol suppression value shown for this subject is unknown. However, no relevant difference to the concentration measured for other subjects in the study Infacort 002 has been shown for all other cortisol concentrations of this subject determined during the 5 treatment periods. **The Applicant has therefore decided to exclude this subject in view of the magnitude of unsuppressed endogenous cortiso**l and its impact on bioequivalence conclusion. In comparison to the study Infacort 001, the Applicant has explained the lack of impact of the inclusion/exclusion of the subjects with inadequate cortisol suppression on the bioequivalence conclusions by the smaller magnitude of the unsuppressed endogenous cortisol than the one observed in the study Infacort 002 for the subject 005. Even if the exclusion of the subject 005 should have been done according to criteria previously described in the protocol of the study, the analysis has been conducted using the 13 subjects and 14 subjects without inadequate endogenous cortisol suppression for the hydrocortisone 20 mg tablet treatment and the Infacort 20 mg treatment, respectively. This is still in accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), where the only criterion on the number of subjects is the minimum number, which is **12 <u>evaluable</u> subjects**. With the number of evaluable subjects still being in accordance with the BE-guideline and the clinical monitoring and individualization of the hydrocortisone dose according to the patient response with the aim to give to the patient the lowest effective dosage, knowing that the 90%CI for AUC is well within this interval and the unmet medical need, it is concluded that the evidence base obtained through the Phase 3 studies is relevant to the proposed hybrid application. The results of the **planned population PK analysis of study Infacort 003** will also help to determine the optimal dosing regimen for this replacement therapy which is available in a dose-appropriate form designed for children. Results using baseline adjusted data <u>excluding</u> individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression were shown in the tables below.

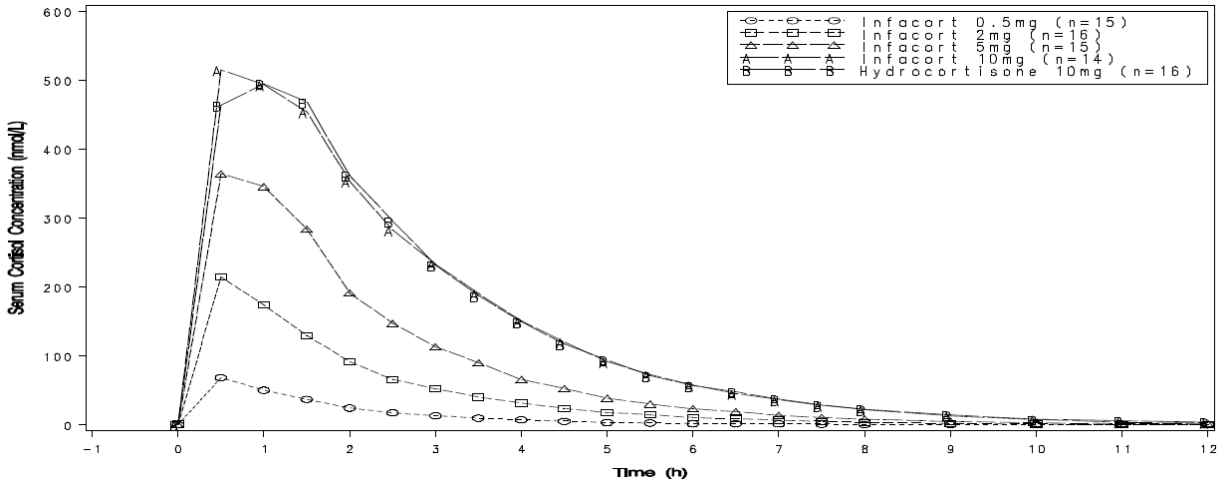

Figure 3: Mean serum cortisol concentration-time curves on a linear scale for oral Alkindi® 0.5 mg (n=15), 2 mg (n=16), 5 mg (n=15), 10 mg (n=14) and hydrocortisone tablet 10 mg using baseline adjusted excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrate inadequate suppression (study Infacort 001)

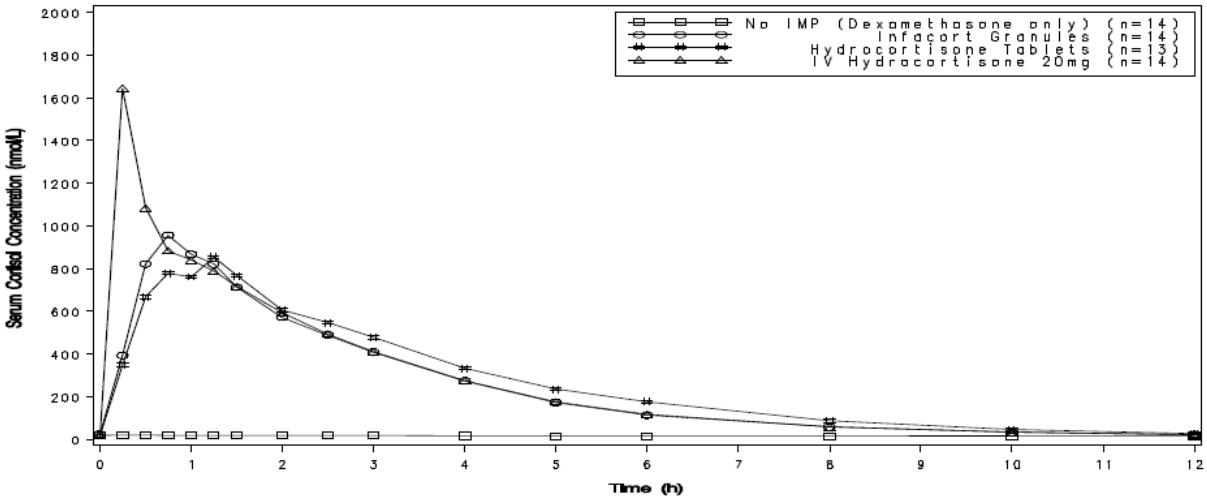

Figure 4: Mean serum cortisol concentration-time curves on a linear scale for oral Alkindi® 20 mg, hydrocortisone tablets 20 mg and i.v. hydrocortisone 20 mg – baseline adjusted excluding individual profiles from subjects where pre-dose cortisol demonstrated inadequate suppression (study Infacort 002)

Table 7: Pharmacokinetic parameters for 10 mg Alkindi® (test) and 10 mg hydrocortisone (reference tablet) using baseline adjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression i.e 2 subjects prior to administration of Alkindi® (non-transformed values) (non-compartmental analysis)(study Infacort 001)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ (hr*nmol/L)	1603.07	281.77	1598.61	245.15
$AUC_{(0-\infty)}$ (hr*nmol/L)	1609.803	285.01	1608.48	251.30
C_{max} (nmol/L)	600.161	138.47	611.07	98.27
t_{max}* (hr)	0.75	0.50-1.50	1.00	0.50-1.50
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
t_{max}	time for maximum concentration (* median, range)			

Table 8: Statistical analysis of bioequivalence between 10 mg Alkindi® (test) and 10 mg hydrocortisone tablet (reference) using baseline adjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression .e 2 subjects prior to administration of Alkindi® (log-transformed values)(non-compartmental analysis - study Infacort 001)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	101.27	95.78-107.09	-
C_{max}	94.71	83.51-107.40	-
* estimated from the Residual Mean Squares			

Table 9: Summary of derived PK for oral Alkindi®, hydrocortisone tablets and i.v. hydrocortisone – baseline adjusted excluding individual profiles from the subject where pre-dose cortisol demonstrated inadequate suppression i.e 1 subject prior to administration of hydrocortisone tablets (non-transformed values) (non-compartmental analysis – study Infacort 002)

PK parameter		Study Period[1]		
		3-4		5
		20 mg Hydrocortisone		
		Oral Alkindi® N=14	Oral hydrocortisone tablets N=13	i.v. solution N=14
C_{max} (nmol/L)	Arithmetic mean SD	973.609 283.773	926.112 258.083	1629.632 491.267
t_{max} (h)	Median range	0.75 0.50-1.25	1.25 0.50-1.50	0.25 0.25-0.25

AUC_{0-t} (h*nmol/L)	Arithmetic mean SD	2629.804 713.757	3002.405 850.306	3056.149 971.404
AUC_{0-inf} (h*nmol/L)	Arithmetic mean SD	2650.841 717.261	3027.262 868.109	3069.489 980.434

[1] Oral Infacort, hydrocortisone tablet and i.v. hydrocortisone were administered to each subject over Study Periods 3-5 (1/period). Each subject received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22.00 on Day 1, and at approximately 06.00 and 12.00 on Day 2.
I.V. = intra venous, IMP = investigational medicinal product, NC = Not calculated

Table 10: Summary of statistical analysis of comparative bioavailability for oral Alkindi (test) vs Hydrocortisone tablet (reference) – baseline adjusted excluding individual profile from the subject where pre-dose cortisol demonstrated inadequate suppression i.e 1 subject prior to administration of hydrocortisone tablets (log-transformed values) (non-compartmental analysis– study Infacort 002)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	89.96	81.72-99.04	
C_{max}	106.83	96.92-117.76	
* estimated from the Residual Mean Squares			

Regarding the bioanalytical methods, the applied LC-MS-MS assay for the determination of cortisol in samples from studies Infacort 001, Infacort 002 and Infacort 003 was properly validated before sample analysis. No interference was observed in the presence of dexamethasone, which was co-administered to subjects in Infacort 001 and 002. The potential interference of prednisolone is actually not an issue, since this compound was not taken by any patient in Infacort 003 (and prescribed drugs are not allowed in Infacort 001 and 002).

The absence of an incurred sample reanalysis in Infacort 001 and Infacort 002 was accepted, taken into account that ISR acceptance was met in Infacort 003, even if reanalysis of solely samples initially analysed in a single batch was not considered to be fully in accordance to the *Guideline on bioanalytical method validation' (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)*.

Despite the fact that the assay was considered sufficiently validated, it was noted in the provided chromatograms that several samples were re-integrated. Reintegration of the chromatograms has been performed according to the procedure described in the SOP. They led to only small adjustments in concentrations or confirmed the absence of a detectable concentration. The impact of the reintegrations on the conclusions was therefore rather limited.

No drug-drug interaction study has been conducted. The Applicant mainly focused on the potential of inhibitors or inducers of CYP3A4 on the PK of Alkindi® and the need for dose adjustment in case of co-administration.

The Applicant has not conducted any studies in patients with impaired hepatic or renal impaired functions. This has been adequately reflected in the SmPC. It was considered acceptable given that the SmPC recommends to dose the patients according to their individual response and to monitor them clinically regardless of renal or hepatic status.

Conclusions on Pharmacokinetics

Even if some uncertainties remained on the bioequivalence conclusions for C_{max} for the studies Infacort 001 and 002, knowing that bioequivalence could be confirmed with regards to $AUC_{(0-t)}$ and taking into account the results from the clinical studies Infacort 003 and 004, it was concluded that Alkindi is therapeutically equivalent to the reference products. In addition, the development of this new formulation with the same type of granules for all capsule strengths fulfilled an unmet medical need in paediatric patients and each dose is individually titrated based on the actively monitored individual clinical response. Altogether, Alkindi was considered to be approvable. CHMP recommended that the results of the planned population PK analysis of study Infacort 003 are submitted in the first quarter of 2018 to help to determine the optimal dosing regimen for this replacement therapy which is available in a dose-appropriate form designed for children; the data analysis plan should be submitted as well. The applicant has committed to address and implement these CHMP Recommendations.

2.4.3. Pharmacodynamics

In study Infacort 002, one of the arms in the 5-arm healthy adult male volunteer crossover study was no treatment, which allowed endogenous cortisol levels to be assessed. These results showed that cortisol exhibits a circadian rhythm in serum, with peak concentrations occurring around 07:00 and the lowest levels occurring at around 24:00. This is in line with the published literature, where **the diurnal pattern of cortisol** is well established. Additional clinical pharmacology testing in study Infacort 002 showed that the same **circadian rhythm for cortisol is seen in saliva**, with peak concentrations for free salivary cortisol and cortisone occurring around 07:00 hours and the lowest levels seen at around 22:00 in saliva (compared to 24:00 hours in serum). Determination of serum cortisol, serum cortisone and free cortisol by a specialist laboratory using liquid chromatography mass spectrometry also showed the same circadian rhythm.

When the free salivary cortisol Cmax was compared for endogenous levels (no treatment), oral Alkindi, IRHC tablets and i.v. hydrocortisone, **values were higher following oral Alkindi (granules in capsules for opening), IRHC tablets and i.v. hydrocortisone compared to endogenous levels**, with the highest Cmax observed following Alkindi treatment. The high levels seen after Alkindi treatment occurred within the first hour post-dose (the majority of which occurred between 15 and 30 minutes post-dose). It is likely that these high readings result from residual matter in the mouth following oral dosing rather than a 'true' measurement of free salivary cortisol. When the salivary cortisone Cmax was compared for endogenous levels, oral Alkindi, IRHC tablets and i.v. hydrocortisone, values following treatment were higher than endogenous levels, with the highest Cmax following i.v. hydrocortisone. No oral contamination of salivary cortisone was observed following treatment with the IRHC tablet and Alkindi. The free cortisol index (FCI), a surrogate biomarker for serum-free cortisol, also increased with salivary cortisone concentrations, thus indicating that serum cortisol has a strong correlation with salivary cortisone after hydrocortisone administration. **Thus salivary cortisone may be a better marker in saliva of circulating cortisol than salivary cortisol itself**.

The PD mechanism of action of hydrocortisone is well documented in the literature and it is known to have profound and varied metabolic actions on carbohydrates, proteins and fat, anti-inflammatory and immunosuppressive functions. Hydrocortisone, in common with other glucocorticoids, binds to the cytosolic glucocorticoid receptor (GR), which is activated by ligand binding. The newly formed receptor-ligand complex translocates into the cell nucleus, where it binds to glucocorticoid response elements (GRE) in the promoter region of the target genes, resulting in the regulation of gene expression. This process is commonly referred to as transactivation. The opposite mechanism is called transrepression. The activated hormone receptor

interacts with specific transcription factors (such as activator protein 1 [AP-1] and nuclear factor kappa B [NF-κB]) and prevents the transcription of targeted genes. **Glucocorticoids (GC) are able to prevent the transcription of pro-inflammatory genes**, including interleukins IL-1B, IL-4, IL-5, and IL-8, chemokines, cytokines, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumour necrosis factor alpha (TNFα) genes. **Glucocorticoids have also been shown to exert a number of rapid actions that are independent of the regulation of gene transcription**. Binding of corticosteroids to the GR stimulates phosphatidylinositol 3-kinase and protein kinase B, leading to endothelial nitric oxide synthase (eNOS) activation and nitric oxide-dependent vasorelaxation.

Membrane-associated GR has been shown to mediate lymphocytolysis.

The physiological effects of cortisol and hydrocortisone are also well documented. Cortisol has widespread actions on metabolism and the functioning of various organs. It is released naturally in response to stress, acting to restore homeostasis in a number of body systems, including glucose metabolism and gastric and renal secretion.

In addition to the effects of cortisol produced by **binding to the glucocorticoid receptor**, because of its molecular similarity to aldosterone it also produces effects by **binding to the mineralocorticoid receptor**. Aldosterone and cortisol have a similar affinity for the mineralocorticoid receptor, however, glucocorticoids circulate at roughly 100 times the level of mineralocorticoids.

These PD effects of Infacort were assessed to a limited extent in study Infacort 002. Cortisol circulates bound to plasma proteins, CBG, and, to a lesser extent, to albumin. Under basal conditions about 5-10% of circulating cortisol is free, about 80% is bound to CBG, and the remainder is bound to albumin. However, **it is the free hormone that is active**. Normal CBG has a cortisol-binding capacity of 25µg/dL, with increases in total plasma cortisol concentrations above this level resulting in rapid increases in levels of free cortisol concentration. The cortisol-binding capacity of albumin is greater than that of CBG, but its affinity is lower. In normal individuals there are **circadian fluctuations in the capacity of CBG for cortisol** which are lost in patients on chronic replacement therapy. Levels of CBG are substantially lower in the plasma of newborn infants than those found in adult subjects or in older children. Total serum cortisol levels are significantly affected by variation in CBG, therefore CBG (and albumin) levels were measured in the Infacort 002 study. Treatment with oral Alkindi, IRHC tablets and i.v. hydrocortisone was shown to have no effect on serum albumin and CBG levels, with similar values reported pre-dose and throughout the sampling period when compared to endogenous levels.

Given the effects of cortisol/hydrocortisone on glucose metabolism, the effects of treatment with oral Infacort, IRHC tablets and i.v. hydrocortisone on glucose levels and insulin sensitivity were evaluated in study Infacort 002. Very little effect on glucose and insulin levels or insulin sensitivity was seen after a single dose of Infacort, IRHC tablets and i.v. hydrocortisone

In addition to the analyses conducted and reported in the main Infacort 002 study report, highly exploratory supplementary studies were conducted by academic groups to determine serum and urine metabolites, using the samples collected within study Infacort 002. Evaluation of metabolites in urine showed that administration of hydrocortisone (Alkindi, IRHC tablet and i.v. hydrocortisone) increased glucocorticoid metabolite excretion into the urine that exceeded endogenous levels of metabolite production. Increased or decreased cortisol levels also induced changes in multiple metabolic pathways, primarily focused on catabolic metabolism, which are primarily regulated by cortisol. Interestingly, all of these metabolite classes were also perturbed following dexamethasone administration, showing an effect of low cortisol levels interacting with high dexamethasone levels. It is important to emphasise the highly exploratory and unconfirmed nature of

the findings, based on data from a very small sample of healthy adult male volunteers measuring a large number of variables in the metabolome.

Metabolomics is a very new, as yet unproven, and developing area in medical science for which the current clinical value and utility is undetermined. The results from this exploratory study show that the metabolome is altered by the glucocorticoids dexamethasone and hydrocortisone, as would be expected. All 3 formulations of hydrocortisone show similar changes in the metabolome, although for Alkindi some of these changes did not reach statistical significance, but this may simply be a reflection of the small number of subjects. Overall, there were not thought to be meaningful differences between the different hydrocortisone preparations, specifically between Infacort and IRHC tablets.

2.4.4. Clinical efficacy

Main clinical study Infacort 003

Hydrocortisone is an established treatment in humans and **has been used as replacement therapy since the 1950s** [Kupperman 1955]. When it was first introduced it was shown to rapidly improve prognosis in patients with AI [Dunlop 1963] and it remains the mainstay for cortisol replacement therapy to this day [Bancos 2014; Martindale 2007]. A global survey of more than 1000 patients, mostly with primary AI, showed that hydrocortisone was the most common treatment (75%), followed by prednisone or prednisolone (11%), cortisone (6%), and dexamethasone (4%) [Forss 2012].

Since **Alkindi (granules in capsules for opening)** is aimed to be bioequivalent to IRHC, its efficacy is expected to reflect that of standard hydrocortisone. In line with the agreed PIP, the only study needed to evaluate efficacy in the target patient population was an **open-label, single dose study in children less than 6 years of age (study Infacort 003)**. Study Infacort 003 started recruitment in March 2015, and recruitment was completed in May 2016. The study was conducted at Charité-Universitätsmedizin Berlin, or at remote satellite sites managed by Charité-Universitätsmedizin Berlin, **in a total of 24 paediatric patients under the age of 6 years with diagnosed AI**. Each child received a single oral dose of Alkindi based on their previously administered standardised dose of hydrocortisone. Serum cortisol measurements from the 1-hour sample were taken as representative of peak values and those from the 4-hour sample as being the best predictor of the AUC [Mah 2004]. In the oldest age group, **additional samples were taken for population PK analysis**.

2.4.4.1. Study population

At entry into study Infacort 003, male or female subjects aged less than 6 years of age, with a diagnosis of AI (as confirmed by an inappropriately low cortisol level plus any other supporting tests) who had been receiving appropriate adrenal replacement therapy (hydrocortisone with/without fludrocortisone) were enrolled. The exclusion criteria for the trial program were limited to safety issues and so excluded subjects at risk of acute adrenal crisis, those who had an intercurrent illness, or if they were receiving a medication or had an underlying condition that might interfere with the trial procedures. None of these are thought to have a major impact on the target population, as any serious intercurrent illness, particularly if leading to inability to take oral medication, would indicate possible adrenal crisis and the patient would be switched to parenteral hydrocortisone therapy as per usual practice in paediatric endocrine centres.

The median ages of subjects entered into study Infacort 003 were in line with the recommended age cohorts of the study: **median age of 1197.0 days (approximately 3 years, 3 months) in Cohort 1 (protocol defined as subjects 2 years to <6 years), 496.5 days (approximately 1 year, 4 months) in Cohort 2 (protocol defined as subjects 28 days to <2 years), and 23.0 days in Cohort 3 (protocol defined as subjects <28 days)**. The majority of subjects (95.8%) were diagnosed with CAH, which reflects the usual diagnosis of AI in paediatric patients. Approximately half the subjects were male, which again reflects the expected trend in this population.

All of the subjects entered into study Infacort 003 were white, which reflects the predominant ethnicity of the patient population attending the study centre in Berlin, Germany. However, there is no indication that other ethnic groups would respond any differently to oral hydrocortisone.

2.4.4.2. Serum cortisol concentrations (primary endpoint)

In study Infacort 003, **the primary endpoint was the maximum level of serum cortisol concentration up to 240 minutes after intake of study drug** (using samples taken at 0, 60 and 240 minutes post-dose), as determined by the **central laboratory**. This endpoint of cortisol levels is **the usual measurement in clinical practice** for ensuring that patients with AI are receiving sufficient cortisol replacement for exogenous hydrocortisone dosing. **The Cmax was observed at 60 minutes post-dose in each cohort** and this was selected as a representation of the peak values (although this may reflect the sampling times rather than the true Cmax).

At Cmax a statistically significant increase was seen in cortisol levels compared to baseline for all cohorts combined (p<0.0001). Thus the primary endpoint of the study was met. When each cohort was analysed separately, a statistically significant difference compared to baseline was seen in Cohort 1 (p=0.0005), but for Cohorts 2 and 3, although all subjects showed an increase in cortisol, the difference from baseline was not statistically significant (p=0.0313 at the 1% level). This lack of statistical significance is likely to be due to the low number of subjects and it should be noted that the study was not powered to determine a difference in the individual cohort.

A secondary analysis of the serum cortisol levels was conducted using the paired t-test to assess the sensitivity of the data to a different statistical test, with these results reflecting those seen in the primary analysis, thus demonstrating the robustness of the study results. **At Cmax (i.e. 60 minutes after Alkindi dosing), serum cortisol levels were ≥150nmol/L in all 24 subjects, with the level of 150nmol/L (5.2 µg/dL) being reported as the median cortisol level in adults.** It has been suggested [Mah 2004] that **adult patients should be dosed at a level to achieve a peak plasma cortisol concentration in the range 400-1000nmol/L at 60 minutes post-dose**, since this level is thought to be associated with optimal replacement therapy. In study Infacort 003, **mean peak values at 60 minutes post-dose were 597nmol/L** (based on the central laboratory analysis), thus achieving the limits set by Mah.

The second timepoint analysed in this study was 4 hours post-dose, which is thought to be the best predictor of the AUC [Mah 2004]. When all cohorts were combined, the overall change at 240 minutes was still significantly greater than baseline (p=0.0026), but again when analysed by cohort, Cohorts 2 and 3 did not show a statistically significant difference from baseline. This was also reflected in the categorical analysis, where at 240 minutes after dosing, 10 subjects (43.5%) had serum cortisol levels <50nmol/L, 10 subjects (43.5%) had levels of 50 to <100nmol/L, 1 subject (4.3%) had a level of 100 to <150nmol/L, and 2 subjects (8.7%) had levels ≥150nmol/L (only 23 subjects had evaluable data at this timepoint). However, the number of subjects in each cohort was low and these cohorts were not individually

powered for statistical significance. In addition, it is known that there is wide inter-individual variability in cortisol AUC following administration of oral hydrocortisone, with the time taken to reach a plasma concentration of <100nmol/L being documented as 289 minutes (range 140 -540 minutes). It is also known that **children treated with hydrocortisone experience several spikes in cortisol concentrations throughout the day, but this is not associated with any acute detrimental clinical endpoints such as hypoglycaemia, lethargy, or change in cognitive function.** Food can also play a part in delaying hydrocortisone absorption and so prolong the response, so the fasting required pre- and post-dosing in this study may also have been responsible for the quicker absorption of Alkindi. Thus it is difficult to attribute clinical significance to these findings.

In study Infacort 003, **serum cortisol concentrations** were evaluated for the primary analysis using **i.v. sampling** and the results were analysed by the **central laboratory** using liquid chromatography-tandem mass spectrometry (LC-MS-MS) methods. In addition, i.v. samples were analysed by the **local laboratory** at baseline and 60 minutes post-dose as a safety measure using radioimmunoassay kits to ensure all subjects achieved adequate cortisol levels post-dose. In addition, **blood spots** were analysed using LC-MS-MS for a range of hormones at the **local laboratory** as an exploratory safety measure. A summary of the change from baseline for all these results is provided in Table 11.

All the results showed the same trend, with high cortisol levels being seen in all 3 cohorts at 60 minutes post-dose, but with levels falling to near baseline levels by 240 minutes post-dose. **The youngest children in Cohort 3 showed the highest levels at both 60 and 240 minutes post-dose**, which is probably related to clinical practice where neonates are usually given a higher dose per body weight compared to older children to stabilise their cortisol levels. This is supported by the fact that the neonates in Cohort 3 received a median dose of 2.0mg, which was the same median dose as the older infants in Cohort 2 (see Table 10 in Infacort 003 CSR). This practice of a higher initial dose in neonates is in line with the *Lawson Wilkins Paediatric Endocrine Society* and *The European Society for Paediatric Endocrinology Guidelines* that suggest during infancy an initial reduction of markedly elevated adrenal sex hormones may require up to 25/m2/day hydrocortisone. Although the results using the different methods showed the same pattern, it is of note that the results for serum cortisol using the local laboratory were higher than those recorded by the central laboratory. This is likely to be attributable to different methodologies used by the 2 laboratories for the analysis, since **the central laboratory used LC-MS-MS** and **the local laboratory used radioimmunoassay**. **The LC-MS-MS method is the gold standard method for steroid analysis** and has high sensitivity and specificity, but not all local laboratories have this equipment. Thus it is an important point for clinicians to note when hydrocortisone is titrated to a dose that sustains the serum cortisol levels within a set range, that different analytical methods can provide different absolute values. It is also of note that **the results using blood spot analysis were notably lower than the results obtained using venous samples**. The blood spot methodology is still exploratory and is not yet fully validated, but the aim was to see if cortisol levels could be adequately assessed using blood spots rather than having to take venous samples. This exploratory technique of blood spot analysis has been used in research studies in infants and has also been successfully taught to parents and used in the home to monitor paediatric cortisol levels in one study**. The blood spot data from the Infacort 003 study, along with the blood spot data collected at the end of the Infacort 004 study will therefore be combined and analysed at a later date;** initial indications are that, possibly with the application of a conversion factor, cortisol levels could be monitored in the future using blood spot analysis.

Table 11 Mean change from baseline in cortisol levels in protocol Infacort 003 (PK Population) Infacort 003

	Infacort 003			
	Cohort 1[1]	Cohort 2[1]	Cohort 3[1]	Overall
Mean (SD)	N=12	N=6	N=6	N=24
Central laboratory venous samples				
60 minutes	523.9 (87.71)	414.8 (86.94)	925.4 (473.88)	597.0 (306.14)
240 minutes	35.6 (27.03)	16.4 (74.78)	95.7 (194.99)	47.1 (104.66)
Local laboratory venous samples				
60 minutes	704.6 (102.18)	625.2 (151.53)	1085.5 (327.21)[2]	766.7 (246.10)[3]
Local laboratory blood spot samples				
60 minutes	87.6 (20.92)	66.7 (22.26)	379.8 (274.91)	159.3 (188.40)
240 minutes	8.1 (5.67)	2.3 (11.16)	36.8 (73.04)	14.3 (37.99)

1 Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days
2 n=5
3 n=23
SD=standard deviation

2.4.4.3. Palatability (secondary endpoint)

In studies Infacort 001, 002 (in healthy adults) and 003 (paediatric with AI) all patients were asked to complete an age-appropriate assessment of acceptability and palatability [based on Davies 2008].

In the heathy adult studies, the majority of subjects described Alkindi as 'not good or bad' for smell (78.6-87.5% of subjects), feel in the mouth (42.9-68.8% of subjects) and taste (57.1-81.3% of subjects), with 42.9-81.3% of subjects describing the taste as 'neutral'. One adult subject did not like the taste of the Infacort granules and reported an adverse event (AE) of dysgeusia following the 2mg Infacort dose and nausea after taking the 0.5mg dose.

In study Infacort 003, Alkindi was positively received by parents/carers, with 82.6% of parents/carers agreeing or strongly agreeing that their child found swallowing easy; 65.2% agreed or strongly agreed that their child showed a positive reaction after Alkindi was given; 95.5% would be happy to give their child Alkindi in the future; and 95.5% preferred Alkindi to the usual hydrocortisone medication. Positive responses predominated in all cohorts, even in Cohort 3 where subjects were aged <28 days: in this cohort all 6 of the parents/carers would be happy to give their child Alkindi in the future and all 6 preferred Alkindi to the usual hydrocortisone medication. In study Alkindi 003, 6 of the 12 subjects in Cohort 1 completed a palatability questionnaire (these 6 subjects ranged in age from 2.6 years to 4.7 years). The subjects generally gave positive or neutral responses to the questions. It should be noted that the questionnaires used in this study were developed by the Sponsor for this study and are not validated in any way. There is a lack of validated questionnaires for the assessment of patient reported outcomes in children <5 years, and assessing patient perception in pre-school children is difficult.

Although the majority of responses were neutral or positive, some subjects did not like the taste, with this being attributable in some cases to the granules sticking in the mouth and so the taste-masking layer of the granules wearing off before the granules were swallowed. It is also of note that in the extension study Infacort 004, 6 subjects withdrew from the study at the request of the parents/carers. In addition, one child refused even to try the medicine at the first visit. This issue was investigated, and the withdrawals were attributable to the 8-hourly dosing regimen used by this centre, which means that the children had to be woken up late at night for their last dose.

Historically, these children received their night-time dose of hydrocortisone as an extemporaneously prepared sweetened liquid via a syringe which generally did not result in the child being woken up to full consciousness. When this regime of night-time dosing was continued in the Infacort 004 study, replacing the locally prepared liquid formulation in a syringe with Alkindi multiparticulate granules, the children had to be woken up to take the Alkindi dose but they were still sleepy and therefore less cooperative and took longer to swallow their dose and so allowed the taste-masking layer to start to dissolve. This problem was seen in older children but did not appear to be a concern for younger children who had not yet become used to any particular approach. Carers were advised to contact a doctor if the patient refused medication and this was done in all cases. Following on from these cases, and based on in vitro data that has recently become available, a protocol amendment was implemented to allow parents/carers to mix Alkindi with yoghurt or fruit purees to facilitate administration, and improve the acceptability and palatability of dosing to children. This sprinkle approach is utilised for many paediatric products.

Since this protocol amendment has been implemented, there have been no further withdrawals from the study. Diurnal is continuing its pre-planned work program of food compatibility testing to permit dosing of the multiparticulate granules with a variety of soft foods.

2.4.4.4. Efficacy data supporting dose selection

There is **no reliable biochemical marker to assess the appropriateness of dose in glucocorticoid replacement treatment**, and so dose modification is guided by clinical judgement and subjective perception of symptoms and signs of glucocorticoid under-replacement and over-replacement. The goal is **to achieve the best clinical result with the lowest possible daily dose of steroid**. Since Alkindi is intended to be bioequivalent to IRHC, it should also be dosed based on the individual needs of the subject, but usually at a dosing interval of 3 times a day.

The lowest possible dosage should be used to avoid unwanted effects as a result of over-exposure to hydrocortisone. **Typical maintenance doses of Alkindi are 8-10mg/m2/day for patients with AI alone and 10-15mg/m2/day in patients with CAH, in 3 divided doses**. This is based on the half-life of hydrocortisone of approximately 100 minutes. In patients with some remaining endogenous cortisol production, a lower dose may be sufficient. This recommended dosing in study Infacort 003 yielded a mean peak plasma cortisol concentration of 597nmol/L, which is within the optimal replacement therapy range suggested by Mah [Mah 2004]. The highest maintenance dose of Alkindi studied in the clinical trials to date is 31mg/m2/day (calculated by extrapolating the single dose exposure in the cohort to a 3 times a day regime as used at the study site). All patients should be observed closely for signs that might indicate dosage adjustment is required, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g. surgery, infection, trauma) since during stress, or when stress is anticipated, it may be necessary to increase the dose temporarily.

Supportive study Infacort 004

2.4.4.5. Long-term efficacy data

Despite **Study Infacort 004 was at an early stage**, and a formal analysis of efficacy had not been conducted, it was noted that overall the children in the study seemed well. In particular, it was of note that no cases of adrenal crisis have been reported, despite, as would be expected in this age group, numerous

intercurrent illnesses being reported that needed a temporary increase in the dose of Alkindi. This preliminary information provided further supportive evidence of the efficacy of Alkindi.

However, **7 of 18 enrolled patients have dropped out** already from study Infacort 004 without detailing the reasons for dropout other than 'withdrawal of consent'. The applicant stated that since changing the method of administration, allowing the product to be administered with soft food or yoghurt, no further dropouts have been reported.

2.4.4.6. Long-term use and development of tolerance

AI is a chronic condition and all subjects will require replacement hydrocortisone for life. There is **no evidence that the efficacy of hydrocortisone changes over time**, thus there is no expectation that the efficacy of Alkindi will change over time, since Alkindi is a paediatric-specific presentation of hydrocortisone and is to be bioequivalent to IRHC (Refer to PK MO and OC).

Only preliminary, unvalidated, **interim safety data were available for study Infacort 004**, **with the mean duration of treatment up to the cut-off date of 26 August 2016 being 102 days** (approximately 3.5 months), with a range from 1-169 days (1 day to 5.6 months). However, there was no indication from the available data that there were any detrimental effects with long-term use or that tolerance develops over time.

2.4.5. Discussion on clinical efficacy

Design and conduct of clinical studies

Study Infacort 003 was designed in line with the recommendations issued by the PDCO in the associated PIP (EMEA-001283-PIP01-12) which served as basis for the development plan supporting current PUMA application. PIP compliance was confirmed by the PDCO in October 2016.

Efficacy data and additional analyses

Infacort 003 was designed **to assess peak and 4 hour cortisol levels in paediatric patients 0-6 year** following a single dose administration of Alkindi identical to the personalised IRHC doses these patients receive. **Palatability was assessed as a secondary endpoint**.

Cmax cortisol levels were in the expected range at 1 hour following the single dose administration, but lower than expected at 4 hours following administration in a substantial number of patients. Since the product was administered in fasting conditions, which are unlikely to reflect daily practice, and a limited food effect on hydrocortisone is reported, cortisol levels might be different when administered with food.

The impact of food on the peak drug level appears to be however limited with the peak drug level under fed conditions representing about 85% of the peak drug level observed under fasting conditions and after administration with 250 ml of water. In addition, **a monitoring of the clinical response** is recommended in the section 4.2 of the SmPC. No food effect related recommendation was available in the SmPC of the reference product Hydrocortisone 10 mg Auden MacKenzie (PL 17507/0246 - study Infacort 001). Therefore, **bioequivalence should preferably be tested under fasting conditions as this situation would be**

more sensitive to difference in pharmacokinetics. The bioequivalence studies Infacort 001 and Infacort 002 were conducted under close to fasting conditions (a light meal or a standard breakfast have been given one hour after drug administration, while the EMA Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr** requires for fasting condition that no food is allowed at least 4 hours post-dose). Finally, the data gathered on efficacy and safety in the phase III clinical study Infacort 004 conducted under real life conditions were reassuring.

It was initially unclear **how palatability data from a single dose study could be extrapolated** to reflect long term triple daily administration of the product. In addition, palatability was assessed in study Infacort 003 using non-validated questionnaires, so uncertainties on the general validity of these data were raised. The palatability questionnaire used in study Infacort 003 was not used in study Infacort 004, since Infacort 004 was primarily designed as a safety study but practical experience from study Infacort 004 suggested that palatability might be less an issue than initially feared, as the administration was proposed to be modified on a patient per patient basis ensuring proper administration according to the patient's preferences. It was noted that 2 patients dropped out of study Infacort 004 because they refused or spat out the medicine at the first visit, 5 others dropped out since the night time dosing schedule they were used to, could not be transposed onto the use of Alkindi as it interfered with the willingness to take up the medicine and the child's sleeping pattern. 11 patients have since been taking Alkindi for about one year.

The choices open to parents/carers to administer Alkindi either as dry granules washed down with fluid, or sprinkled onto soft foods, increase the acceptability of dosing of a medicine *per se* in this challenging age group and is expected to enhance palatability where necessary. The method of administration implies the use of yoghurt or fruit puree in children older than 6 months. Following practical experience, the method of administration in the SmPC was updated which now prefers **sprinkling of the medicine onto soft food rather than mixing it**, to further minimise palatability issues.

It was considered that this approach should minimise palatability issues as much as possible in practice, as there were no further dropouts from the study reported further to the 5 patients that dropped out because of issues with the night time dosing. In the worst case scenario, it is however possible that these 5 patients represent the fraction of patients with most uptake issues for which none of the administration modifications would have made a difference. Nevertheless, this appeared hard to prove or to predict.

2.4.6. Conclusions on clinical efficacy

The pivotal efficacy study Infacort 003 in children aged <6 years of age with primary adrenal insufficiency (PAI) was conducted in line with the agreed PIP. The patient population recruited in this study was considered representative of the target population. The primary endpoint of the study was met, with a statistically significant increase in serum cortisol levels observed at Cmax (60 min) compared to baseline serum cortisol levels with all subjects having cortisol levels above the clinically relevant limit at Cmax. The results were also supported by secondary analyses. Cortisol levels at 4 hour post administration were lower than projected. Limited long term data from study Infacort 004 support clinical efficacy.

The applicant was requested to discuss how the currently available data could support extrapolation of efficacy and safety to the group of children > 6 years. as there are older children who are either unwilling or unable to swallow a solid tablet dose form and for whom, in the current treatment paradigm, oral dosing will require compounding the hydrocortisone tablets, which may result in lack of dosing precision. In addition dosage is individualised according to the clinical response of the individual patient. The applicant stated that bioequivalence to the well-established reference product has been confirmed using 10 mg and 20 mg doses and suitable strengths of Alkindi (0.5mg, 1mg, 2mg and 5mg) are available for use by older and therefore

larger children dosed on a mg/m2/day basis, and thus it was considered that the current dataset could be extrapolated to the >6 year-old paediatric age groups where clinically appropriate. The CHMP confirmed that current data do support the use also in children 6 year and older based on adult PK data and experience in the 0-6 year age patient group. Therefore the therapeutic indication was amended as follows: R*eplacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old*).

Palatability questionnaires showed that Alkindi was positively received by healthy volunteers, parents/carers of paediatric subjects, and by the paediatric subjects themselves where subjects were old enough to respond to a specific questionnaire. It is of note that 95.5% of parents/carers would be happy to give their child Alkindi in the future and 95.5% preferred Alkindi to the usual hydrocortisone medication. Limited data from Infacort 003 do point to possible palatability issues in the long term.

2.4.7. Clinical safety

Immediate-release oral tablets of hydrocortisone have been approved and marketed worldwide (including in all EU countries) for more than 50 years and **the safety profile of hydrocortisone immediate-release oral products has been extensively established** [Martindale 2007]. As the physiological roles of cortisol are fundamentally similar at all ages, there were no grounds for supposing that appropriately-dosed replacement therapy will exhibit any differences in safety between adults and children or between different paediatric age subgroups. Also, given that the doses of hydrocortisone in all the studies produced serum cortisol concentrations that encompassed the physiological range, no new safety concerns were envisaged.

The risks associated with Alkindi use described in the following sections have been tailored to those associated with the use of hydrocortisone at replacement therapy levels, rather than including all effects associated with high therapeutic dosing as well. This should help to identify those risks that are most relevant to the use of Alkindi as replacement therapy in children.

2.4.7.1. Adverse effects characteristic of the pharmacological class

Hydrocortisone is a naturally-occurring glucocorticoid hormone secreted by the healthy adrenal cortex. The goal of therapy in patients with AI is to replace this hormone to physiological levels in conditions where it is deficient. Such replacement therapy has been a routine part of medical care in both adults and children for more than 50 years and its safety profile is well understood [Martindale 2007]. Class effects of corticosteroids are well established and are dose-related.

Although well established at high or therapeutic dose, the interactions and side-effects are not so commonly seen at replacement doses of steroids in patients lacking innate steroid secretion. In the SmPC for the reference medicinal product (IRHC manufactured by Auden Mckenzie PL 17507/0246), the adverse effects were separated into those associated or potentially associated with replacement therapy (and therefore applicable for Alkindi) and those associated or potentially associated with use of high therapeutic doses (and therefore not considered applicable for Alkindi and therefore was not included in the SmPC.

2.4.7.2. Relevant animal toxicology and product quality information

No non-clinical safety pharmacology studies have been performed with Alkindi owing to the well-established use of hydrocortisone in humans. A summary of published non-clinical data for hydrocortisone was provided,

with the results showing no unexpected toxicity findings. There were no product quality issues that would be likely to impact on the safety of Alkindi.

2.4.7.3. Safety population and extent of exposure

Four clinical studies contributed safety data in this dossier. Two of the studies (Infacort 001 and Infacort 002) were single dose studies in healthy adult male volunteers, and 2 clinical studies (Infacort 003 and Infacort 004) were conducted in neonates, infants and children less than 6 years of age. Infacort 003 was a single dose study and Infacort 004 was a long-term multiple dosing extension study to allow subjects treated in Infacort 003 to continue treatment. Safety was evaluated in all 4 clinical studies by the collection of adrenal crisis events; implementation of sick day rules; occurrence of AEs, serious adverse events (SAEs), and AEs leading to treatment withdrawal; and changes in vital signs, safety laboratory parameters, and electrocardiograms (ECGs), where evaluated.

Studies Infacort 001 and Infacort 002 were single dose crossover studies in 30 healthy adult male volunteers and used single doses of Alkindi at 0.5mg, 2mg, 5mg, 10mg and 20mg. Study Infacort 003 was also a single dose study in which 24 children with AI were given a single dose of Alkindi at the same dose as their usual IRHC. The median individual doses of Alkindi were 2.50mg in Cohort 1 (children aged 2 years to <6 years), 2.00mg in Cohort 2 (children aged 28 days to <2 years) and 2.00mg in Cohort 3 (infants aged <28 days). The only study to evaluate multiple dosing was study Infacort 004, in which subjects were dosed with Alkindi 3 times a day. To date, 18 subjects have been enrolled in this study, of which 17 have been treated (1 subject refused the first dose and so was withdrawn from the study) and 11 subjects continuing in the study following the withdrawal of additional 6 subjects.

The safety database on Alkindi itself is limited, with data collected on 30 healthy volunteers and 24 subjects <6 years of age with AI. However, since Alkindi is a new formulation of the established IRHC, and given the proposed bioequivalence of Alkindi to IRHC, this safety database is considered sufficient to demonstrate that treatment with Alkindi does not raise any new safety issues compared to IRHC. Interim data from study Infacort 004 provided some preliminary longer-term data after a mean of 102 days treatment (range 1-169 days) up to the cut-off date of 26 August 2016.

No subgroup analyses were performed regarding the safety data due to the small number of AEs reported.

2.4.7.4. Summary of common and non-serious adverse events

In the healthy volunteer studies, the only treatment-emergent adverse event (TEAE) that occurred in more than 1 subject treated with Alkindi was oral hypoaesthesia, with this being reported by 2 subjects following administration of 10mg Alkindi. Both events were considered mild and of probable relationship to the study medication since the events were thought to reflect increased oral sensitivity to the larger number of granules administered at the 10mg Alkindi dose level. Other treatment-related AEs reported in the healthy volunteer studies were 1 subject who reported mild dysgeusia immediately after taking the 2mg dose of Alkindi and mild nausea immediately after taking the 0.5mg dose of Alkindi. No action was taken for either of these AEs and the subject recovered from these events. In study Infacort 001, where 4 dose levels of 0.5mg, 2mg, 5mg and 10mg Alkindi were used, there did not appear to be any dose-related changes in the TEAE profile.

The most common TEAEs reported following a single dose of Alkindi in subjects with AI (study Infacort 003) were diarrhoea (3 subjects, 12.5%), vomiting, and rash (2 subjects, 8.3% for each TEAE). The majority of

the events were considered mild, with only 1 subject reporting moderate events (moderate vomiting and moderate fatigue). None of the events were considered related to Alkindi treatment and all of the events are typically seen in young children.

In study Infacort 004, where repeated dosing of Alkindi was carried out, the most common TEAE was pyrexia, which occurred in almost half of the subjects (47.1%). In the majority of these cases the pyrexia was associated with a concomitant infection such as a viral infection, bronchitis, otitis media and nasopharyngitis and in all cases the dose of Alkindi was increased to prevent an adrenal crisis. All subjects recovered from the pyrexia and none of the events were considered related to Alkindi treatment. Five TEAEs reported in 2 subjects were considered of moderate severity: 1 subject reported moderate tooth injury, stomach ache and nausea, and another subject reported moderate bronchitis and pyrexia.

No cases of subjects choking on the granules were reported. No TEAEs of adrenal crisis were reported in any of the studies. As noted above, 8 subjects in study Infacort 004 had their dose of Alkindi temporarily increased when the child developed a fever, associated in most cases with an infection. This is usual clinical practice in the event of illness to prevent an adrenal crisis occurring and is in line with the sick day rules that are issued to the parents/carers of all children with AI. No subjects were withdrawn from the study due to an AE. No special approaches are needed for the monitoring of AEs with Alkindi beyond those that are used in routine clinical practice.

2.4.7.5. Serious adverse events

No subjects in any of the studies reported an SAE or died during the study.

2.4.7.6. Clinical laboratory findings

In studies Infacort 001 and Infacort 002, routine biochemistry, haematology and urinalysis profiles were evaluated for safety purposes. On several occasions isolated values were seen outside of the study centre's normal ranges but none of these were considered to be clinically significant in the opinion of the examining physician.

In studies Infacort 003 and 004, routine safety biochemistry, haematology and urinalysis profiles were not evaluated. In study Infacort 003, cortisol levels were assessed at the local laboratory 60 minutes after dosing with Alkindi to ensure adequate cortisol levels were achieved, with this being seen in all subjects.

No changes in laboratory parameters in any study were reported as an AE.

2.4.7.7. Other safety observations

Isolated vital signs and ECG values outside of the study centre's normal ranges were seen in the studies where these were measured, but none of these changes were considered to be clinically significant in the opinion of the examining physician. No changes in vital signs or ECGs in any study were reported as an AE. No changes in vital signs or ECG parameters have been reported in the published literature following use of hydrocortisone.

2.4.7.8. Methods to prevent, mitigate, or manage adverse events

Adrenal crisis occurs in patients with AI who have an intercurrent illness or stress. Adrenal crisis is a life-threatening emergency and therefore prevention is of key importance. The frequency of adrenal crisis in

patients with AI has been reported as 6-8 for 100 patient years, with about half of patients with AI reporting at least one previous adrenal crisis. The most frequent precipitating causes are gastroenteritis and fever (60-70%), but other stressful events can also cause crises, such as trauma, surgery, a dental procedure, and major psychological distress.

No events of adrenal crisis were seen in the Alkindi clinical studies. Where events that could lead to an adrenal crisis occur, they can be managed by the implementation of sick day rules. These sick day rules are given to all patients and describe the procedure in the event of an intercurrent illness, which usually involves additional doses of hydrocortisone. This is usual clinical practice for patients receiving hydrocortisone replacement therapy.

Although the majority of responses to the palatability questionnaire were neutral or positive, some subjects in Cohort 1 (aged 2 to 6 years of age) who completed the children's questionnaire did not like the taste, particularly if the granules stuck in the mouth and so the taste-masking layer of the hydrocortisone wore off before the granules were swallowed. Previously it was advised that the granules were washed down with water, breast milk, formula milk or whole milk. However, new in vitro food compatibility studies have been conducted, and it was agreed that 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.

2.4.7.9. Overdose, dependence, rebound effects, or drug abuse

Reports of acute toxicity and/or deaths following hydrocortisone overdose are rare. Overdose or prolonged use of hydrocortisone (in common with other corticosteroids) can exaggerate some of the normal physiological actions of cortisol leading to mineralocorticoid and glucocorticoid side-effects. Mineralocorticoid side-effects include hypertension, sodium and water retention, and potassium and calcium loss. These side-effects can be significant with hydrocortisone.

Glucocorticoid side-effects include diabetes and osteoporosis (particularly in the elderly). Muscle wasting (proximal myopathy) may also occur. Corticosteroid therapy is also weakly linked with peptic ulceration and perforation. High doses of corticosteroid can cause Cushing's syndrome with moon face, striae and acne. In children, administration of corticosteroids may result in the suppression of growth.

No cases of overdose were reported in any of the clinical studies. As noted in the Alkindi SmPC the biological half-life of hydrocortisone is approximately 100 minutes. No antidote is available.

Treatment is probably not indicated for reactions due to chronic overdosing unless the subject has a condition that would render him/her unusually susceptible to ill effects from hydrocortisone. In which case, symptomatic treatment should be instituted as necessary and if necessary hydrocortisone can be removed by dialysis. Anaphylactic and hypersensitivity reactions may be treated with adrenaline, positive-pressure artificial respiration and aminophylline.

AI is a chronic condition and all subjects will require replacement hydrocortisone for life so dependence is not a real consideration. However, there are no data to suggest that hydrocortisone has dependence potential.

Since Alkindi was considered to be bioequivalent to IRHC, no withdrawal or rebound effects were anticipated when Alkindi treatment was switched to IRHC treatment or vice versa. Psychological effects have been reported on withdrawal of corticosteroids, but the relevance of this to withdrawal of Alkindi is unlikely in view of the indication (replacement therapy).

Drug abuse was not expected with Alkindi. No studies have been undertaken to investigate the dependence potential of Alkindi.

2.4.8. Discussion on clinical safety

The safety profile of Alkindi, in the low number of patients included in Infacort 003, was in line with the historical experience with IRHC. No choking events have been reported.

The statements regarding high therapeutic dosing that are included in Special warnings and precautions for use section of the SmPC of the reference medicinal product were removed from the product information of Alkindi during the procedure as high therapeutic dosing (e.g. for immunosuppressive or anti-inflammatory effect) is not recommended for Alkindi.

2.4.9. Conclusions on clinical safety

Immediate-release oral tablets of hydrocortisone have been approved and marketed worldwide (including in all EU countries) for more than 50 years and the safety profile of hydrocortisone immediate-release oral products has been extensively established [Martindale 2007]. As the physiological roles of cortisol are fundamentally similar at all ages, there were no grounds for supposing that appropriately-dosed replacement therapy would exhibit any differences in safety between adults and children or between different paediatric age subgroups. Also, given that the doses of hydrocortisone in all the studies produced serum cortisol concentrations that encompassed the physiological range, no new safety concerns were envisaged. The choking risk was further addressed in the RMP.

2.5. Risk Management Plan

Safety concerns

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)

Summary of safety concerns	
	Risk of Central Serous Chorioretinopathy
Missing information	Long Term Use in Paediatric Patients Use in Hepatic Impairment Use in Renal Impairment

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the fact that the current application concerns only population of paediatric patients and paediatric-specific formulation, the CHMP is of the opinion that a separate entry in the EURD list for Alkindi is needed, as it cannot follow the already existing entry for hydrocortisone. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

Disease or condition

Congenital primary adrenal insufficiency (PAI) is the most common aetiology of adrenal insufficiency (AI) in infants and children from birth to <6 years age group for which Alkindi was developed, and is mostly due to congenital adrenal hyperplasia (CAH), which results from a deficiency in one of several enzymes (most commonly 21-hydroxylase) required for adrenal synthesis of cortisol.

CAH accounts for 95% of AI cases in children and has an incidence of 1:10,000 to 1:16,000 live births in the European and North American populations [Nimkarn 2002]. Symptoms of AI most often develop with combined deficiencies of cortisol and aldosterone and result in androgen excess that clinically manifests in disordered sexual development in girls, precocious pseudopuberty with clitoral and penile enlargement, and short stature, and in adulthood with hirsutism in females and fertility problems in both sexes. With proper treatment and compliance, patients with cortisol deficiency can live a near normal life span without limitations. However, the prognosis for an untreated patient is poor. Death is a common outcome, usually from adrenal crisis precipitated by infection.

Available therapies and unmet medical need

The usual treatment for AI is glucocorticoid replacement using hydrocortisone, which has been a routine part of medical care in both adults and children with AI for more than 50 years. The aim of treatment is to replace cortisol and, in CAH, prevent ACTH-driven androgen excess [Dauber 2010].

This is challenging, since therapy aimed at normalising ACTH and reducing androgen levels can result in excess glucocorticoid exposure with associated complications including short stature, obesity, hypertension and an adverse metabolic profile. Striking the balance between too much and too little glucocorticoid treatment is especially difficult as currently available glucocorticoid formulations cannot replicate the circadian rhythm of cortisol secretion and are not formulated for the paediatric population. Thus adult hydrocortisone tablets have to be ground to a powder by a pharmacist and the estimated dose encapsulated and provided to the parents, who must then try to administer the bitter-tasting crushed tablet as best as they can. This leads to imprecise dosing and the associated risks of under- or over-dosing.

Main clinical studies

This application concerns a hybrid version of hydrocortisone tablets. The reference product Hydrocortisone 10mg Tablets is indicated for use as re-placement therapy in primary, secondary, or acute adrenocortical insufficiency and preoperatively, and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenocortical reserve. Nonclinical studies have not been provided for this application and this was not considered necessary. From a clinical perspective, this application did contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance.

Two bioequivalence studies Infacort 001 and Infacort 002 have been conducted in healthy adult male volunteers to compare the pharmacokinetics of the new formulation Alkindi 2x5mg and 4x5mg with hydrocortisone immediate release tablets 10 mg and 20 mg, respectively. The dose proportionality of Alkindi at doses of 0.5 mg, 2 mg, 5 mg and 10 mg was also investigated in the study Infacort 001. Another primary

aim of the study Infacort 002 was to determine the absolute bioavailability of cortisol from Alkindi granules and hydrocortisone tablets using intravenous hydrocortisone as the reference injection.

The main clinical efficacy study was Infacort 003 in neonates, infants and children younger than 6 years with PAI, in which Cmax levels of serum cortisol following a single administration was the primary endpoint. Infacort 003 included 24 AI patients and convincingly met the primary endpoint. Palatability was a secondary endpoint in the above study.

Uncertainties and limitations about favourable effects

Quality

To mask the bitter taste of hydrocortisone, the granules are coated with a taste-masking layer. The originally proposed dissolution test did not demonstrate that the taste-masking layer is effective and consistent from batch to batch. This issue was considered resolved since an additional dissolution test was developed by the applicant to control the taste mask coating.

Pharmacokinetics

Even if some uncertainties remained on the bioequivalence conclusions for C_{max} for the studies Infacort 001 and 002, knowing that bioequivalence has been shown for $AUC_{(0-t)}$ and taking into account the results from the clinical studies Infacort 003 and 004, it was concluded that Alkindi is therapeutically equivalent to the reference products. In addition, the development of this new formulation with the same type of granules for all capsule strengths responds to an unmet medical need in paediatric patients and each dose should be individually titrated based on the actively monitored individual clinical response. The results of the planned population PK analysis of study Infacort 003 that is planned to be submitted post-authorisation will help to determine the optimal dosing regimen for this replacement therapy which is available in a dose-appropriate form designed for children.

Clinical

The new formulation was developed to ensure proper dosing and replacement therapy for children with AI, from birth on. In the drug development program presented in the PIP, it was stated that the pharmacokinetic data collected in the adult healthy volunteers studies will be used to determine a dose (in terms of mg/m^2 of body surface area) that can be expected to yield both (i) a peak plasma cortisol concentration in the range 400-1000 nmol/l and (ii) a concentration at 4 hours post-dose of 100-300 nmol/l. These were the values found by Mah et al (2004) to be associated with optimal replacement therapy. **The observed cortisol levels at 4 hour following dosing were lower than projected** and could theoretically point to efficacy concerns of the product; however no such signals were observed in the long term study Infacort 004.

Palatability was another important aspect identified in the efficacy testing of the new hydrocortisone formulation. Hydrocortisone by itself has a bitter taste, therefore, the granules are coated with a taste-masking layer. Palatability was tested in the target population through company developed questionnaires, either for carers/parents or for the patients in cohort 1 aged >2 to 6 years. The questionnaires' results were considered encouraging. However, it was unclear whether there has been a formal quality testing of these questionnaires, which were developed specifically for the Infacort 003 study. Such testing would at least add some validity to the questionnaire results, as for now it is unclear to what extent these questionnaires capture the full palatability spectrum as experienced by patients and carers/parents. The issue was considered resolved since long term data from study Infacort 004 indicated that a patient-tailored method of

administration is the preferred approach to ensure adequate uptake of the medicine by the young patients. A major drawback of the current program is **the absence of long term palatability data**. The shear nature of the disease implies lifelong, multiple daily administrations of hydrocortisone. Therefore, palatability conclusions based on the administration of a single dose only were considered insufficient to support long term treatment recommendations for hydrocortisone granules. The applicant was asked to list and discuss long-term palatability issues already encountered in clinical study Infacort 004 and all actions undertaken to address these. In addition, long term (1 year) Infacort 004 palatability data were provided and reviewed in the subsequent steps of the MAA procedure. There was no formal palatability testing in study Infacort 004. However, by applying a patient-tailored method of administration, adequate uptake of the medicine could be ensured.

Long-term experience with Alkindi administration in study Infacort 004 did not indicate that **administration with soft food or washing down with liquid** would interfere with efficacy of the treatment. Fasting was imposed pre and post dosing in study Infacort 003. In study Infacort 004 and in the agreed SmPC, **administration of the drug sprinkled over food was supported.** However, such administration is not applicable in the youngest age group, i.e. neonates and infants 0-6 months. The *EMA Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)* states that powders and granules may be given to children from birth provided they can be administered as a liquid preparation. This would enhance safety and ease of administration compared to current clinical practice. The applicant was asked to comment whether administration of granules suspended in a small volume of liquid can be recommended for neonates and infants 0-6 months, taking into account the effect on the taste-masking coating, and administration problems encountered in daily practice in the youngest patient group. Following the experience with administration of the study drug in the long term study Infacort 004, it was recommended to sprinkle the drug onto soft food for administration in the older segment of the patient group (6 months to 6 year), in case this was considered to improve drug administration. In the youngest patient group, 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. In both patient groups administration is immediately followed by washing down with liquid. The experience from study Infacort 004 indicated that both methods were suitable for administration and no safety issues related to the method of administration were detected in this small patient group.

It should be noted that Alkindi has not been studied in pre-term infants. Pre-term infants born with AI would need replacement hydrocortisone and there was no evidence to suggest that Alkindi would present a greater risk in this age group compared to neonates and older children. However, caution is recommended in treating this age group. The product is contra-indicated in pre-term patients where oral feeding has not yet been established.

The applicant was requested to discuss how the currently available data could support extrapolation of efficacy and safety to the group of children > 6 years as there are older children who are either unwilling or unable to swallow a solid tablet dose form and for whom, in the current treatment paradigm, oral dosing will require compounding the hydrocortisone tablets, which may result in lack of dosing precision. In addition dosage is individualised according to the clinical response of the individual patient. The applicant stated that bioequivalence to the well-established reference product has been confirmed using 10 mg and 20 mg doses and suitable strengths of Alkindi (0.5mg, 1mg, 2mg and 5mg) are available for use by older and therefore larger children dosed on a mg/m2/day basis, and thus it was considered that the current dataset could be extrapolated to the >6 year-old paediatric age groups where clinically appropriate. The CHMP confirmed that current data do support the use also in children 6 year and older based on adult PK data and experience in

the 0-6 year age patient group. Therefore the therapeutic indication was amended as follows: R*eplacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old*).

Unfavourable effects

The risks associated with the use of oral hydrocortisone are well established. However, at physiological replacement doses there are no major-concern side-effects of hydrocortisone therapy.

The doses of hydrocortisone used in all the studies submitted in this dossier resulted in serum concentrations that are within the physiological range. IRHC oral tablets have been approved and marketed worldwide (including in all EU countries) for more than 50 years. Alkindi hydrocortisone multiparticulate granules are not considered to present any additional important safety risks when used at physiological replacement doses in paediatric patients with AI.

Whilst there is evidence that Alkindi is absorbed in adults to the same extent as conventional hydrocortisone, investigators should be alert to failure of Alkindi to be absorbed, e.g. if the child vomits or spits out the granules. This may manifest as symptoms of relative AI. This should be treated with supplemental hydrocortisone in the normal clinical manner. Patients should be observed closely for signs that dose adjustment might be required, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g. surgery, infection, trauma). During stress it may be necessary to increase the dose temporarily. It should be noted that these risks are applicable to all forms of hydrocortisone administered to the child and are not Alkindi-specific.

Discontinuation of Alkindi because the child does not like the taste can be considered as a potential risk, as discontinuation of Alkindi without immediate replacement with another hydrocortisone formulation could result in re-emergence of AI symptoms. However, parents of children with AI are aware of the importance of hydrocortisone replacement and are in close contact with their endocrinology team. As such, the risk with Alkindi is no greater than the risk with any other hydrocortisone product, including extemporaneous compounded products.

A possible risk from swallowing Alkindi granules is the risk of choking. Since it has been shown that children above 6 months of age can safely swallow pellets of 2mm diameter, the applicant considers the Alkindi granule diameter of <800µm acceptable to all the age groups planned to be treated with Alkindi and the risk of choking is low. It is also worthy of note that some other products used in neonates for example, used for the treatment of pancreatic exocrine insufficiency in babies, have a granule size of 0.5-1.0mm, which is comparable to the proposed Alkindi product in terms of granule size. This product has been tested in infants and toddlers and has proved to be efficacious and safe with no choking incidents reported [Colombo 2009; Munck 2009]. Thus, the risk of choking is assumed to be negligible and certainly much less than that associated with the current treatment practice of administering crushed tablets. There were no choking events reported in Infacort 003 and 004 studies.

As the Alkindi granules are contained in a capsule, there is a potential risk that parents and carers will inadvertently attempt to administer the capsule to their child rather than opening the capsule and administering the granules. As the capsule is a common pharmaceutical form, ingestion of the capsule would simply provide a delay to the absorption of the hydrocortisone dose by approximately 5 minutes as the capsule disintegrates. Therefore there is no toxicity concern from ingestion of the capsule, but there could be a concern regarding choking. To mitigate this concern, wording and diagrams on the packaging of Alkindi

granules have been proposed, as well as in the SmPC and the patient information leaflet. Routine pharmacovigilance will ensure that any reports of choking are investigated.

Other potential risks that are associated with replacement doses of hydrocortisone include growth retardation, psychiatric effects, effects on bone mineral density, and interactions with some other drugs. Potential interactions associated with therapeutic dose use are infection risk, effects on electrolytes, optic effects, myocardial infarction, comorbidities, fat embolus, hypothyroidism or cirrhosis, effects on spermatozoa mobility, diabetes risk, menstrual irregularities, and anaphylaxis. These risks are more related to high therapeutic doses of corticosteroids and so may not occur at replacement therapy doses of corticosteroids. Also, none of these potential risks are thought to be any greater with Alkindi compared to IRHC tablets.

Uncertainties and limitations about unfavourable effects

IRHC has a longstanding history in the treatment of AI, and is the recommended treatment option in children with AI, with manageable safety risks associated with treatment (Bornstein et al., 2016; Speiser et al., 2010).

There are sparse data on the long term effects and use of the product. The applicant reported the long term (efficacy and) safety data from study Infacort 004. It is acknowledged that, although IRHC is used in the paediatric population for many decades, there are sparse long term data available from clinical trials in the paediatric population. In addition, long term randomised controlled trials in the paediatric population are non-existing. Long term safety data from study Infacort 004, investigating Alkindi treatment in a small patient group for up to one year, have not revealed novel safety issues.

In the Infacort 004 study, for which interim data were presented, 6 out of 18 patients enrolled dropped out of the study because of withdrawal of consent. In two cases there were issues with the administration of the IMP, leaving four subjects for which no reason for withdrawal is known. The CHMP considered this high number of dropouts as worrisome, and the applicant was requested to further comment on the reasons for dropout of these 4 cases that are all part of the older age cohort, >2 to 6 year. In particular, this high dropout rate was in obvious contrast with the high positive response rates reported in Infacort 003 regarding palatability and preference of Alkindi over standard hydrocortisone treatment, suggesting palatability data from a single dose study should not be extrapolated as such to chronic, long term dosing. The applicant explained that the 4 dropouts were due to inadequate night dosing of Alkindi which required the children to be woken up fully in order to ensure adequate uptake of the product. Following this observation, the method of administration was adjusted allowing the medicine to be sprinkled upon food prior to administration resulting in no further dropouts.

Effects Table

Table 12 Effects Table for Alkindi

Effect	Short Description	Unit	Alkindi	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
$AUC_{(0-t)}$	Geometric Mean Ratio Test/Reference (confidence interval 90%)	-	101.27 (95.78-107.09)		Excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression	Infacort 001
			89.96 (81.72-99.04)			Infacort 002
C_{max}		-	94.71 (83.51-107.40)		Excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression Infrequent sampling around t_{max} casted doubts on the measurement of true C_{max} (C_{max} first point of the concentration time curve in about half of the volunteers in each treatment group)	Infacort 001
			106.83 (96.92-117.76)		Excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression (when subject included, IC 90% Cmax : 100.45-129.15) %)	Infacort 002
Cmax	Serum cortisol levels at 60 min post administration	Nmol /l	Higher than baseline ($p<0.0001$)	NA	Fully dependent on PK OC/MO issues Influence of feeding/fasting? Influence of administration with food?	Infacort 003

Effect	Short Description	Unit	Alkindi	Control	Uncertainties / Strength of evidence	References
Palatability	Palatability experienced by patients/carers	questionnaires	Overall positive	NA	Quality of coating (MO) Quality/validation of questionnaires? No long term data available.	Infacort 003
Unfavourable Effects						
Choking risk	Choking risk	---	not observed	NA	Risk is considered low	Infacort 001, 002, 003 , 004

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Hydrocortisone is a well-established and preferred pharmaceutical treatment option for AI in children, including the most prevalent form of PAI, i.e. CAH (Bornstein et al., 2016; Speiser et al., 2010). The benefit-risk of the active substance as such is therefore considered positive in the treatment of PAI in children. Of note, in the Infacort 003 study, 23 of 24 patients were suffering from CAH.

The proposed benefit of Alkindi over current standard IRHC treatment in children 0-6 years with PAI is comprised of two components: a pharmaceutical form which is more suited for administration in this population and which should ensure a more precise dosing.

Alkindi granules and packaging allow for a more precise dosing than current tablet crushing and weighing and is an important aspect of stable IRHC treatment.

The second advantage relates to the administration itself, in which two aspects can be discerned. First, the granule formulation should allow more appropriate administration to paediatric patients, as long as the product can be sprinkled over soft foods prior to administration, in patients from 6 months of age (European Medicines Agency, 2014). The updated SmPC contains clear recommendations on how the product can be safely and efficiently administered, three times daily, in the 0-6 month age group.

The effectiveness and batch to batch consistency of the taste-masking film is now controlled by a specific *in* vitro dissolution test and adequacy of the taste masking film when the granules are mixed with soft food was demonstrated by *in vitro* data.

Some uncertainties remained on the bioequivalence conclusions between Alkindi and hydrocortisone 10 mg and 20 mg reference tablets for C_{max}. However, since the IC 90% around the geometric LS means ratio T/R for 10 mg and 20 mg hydrocortisone orally administered doses are within the acceptance range 80-125 % for the primary parameters AUC_{0-t} and considering the clinical monitoring in place and the individualization of the hydrocortisone dose according to the patient's response, with the aim of giving the patient the lowest effective dose, the clinical impact of this observation was considered limited. Furthermore, when considering

the impact of this observation, it should be kept in mind that this application does concern a hybrid application in accordance with article 10(3) of the Directive 2001/83/EC and relies thus also in part on the results from the clinical studies Infacort 003 and 004.

Balance of benefits and risks

IRHC is the current standard of care for the envisaged patient population. For the youngest patient group, i.e. 0-6 year of age, a more suitable pharmaceutical form of the product, replacing crushed tablets, is welcomed in terms of more precise dosing and palatability (masking of bitter taste).

In addition current data **do support the use in children 6 year and older based on adult PK data and experience in the 0-6 year age patient group**. There are older children who are either unwilling or unable to swallow a solid tablet dose form and for whom, in the current treatment paradigm, oral dosing will require compounding the hydrocortisone tablets that may result in lack of dosing precision. Therefore also these patients could also benefit from the administration of Alkindi. Therefore it was proposed to amend the therapeutic indication as follows: R*eplacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old*). This updated wording was accepted by the applicant.

The coated IRHC granules in present application do allow for a very precise and reproducible dosing. **Palatability issues** that were reason for concern at first appeared to be adequately dealt with, and the SmPC now contains clear recommendations concerning the method of administration in the respective age groups. Effectiveness and batch to batch consistency of the taste masking coating are now controlled by a specific *in vitro* dissolution test.

Even though some uncertainties remained on the bioequivalence conclusions for C_{max} for the studies Infacort 001 and 002, knowing that bioequivalence can be concluded for $AUC_{(0-t)}$ and taking into account the results from the clinical studies Infacort 003 and 004, it is concluded that Alkindi is therapeutically equivalent to the reference products. In addition, the development of this new formulation with the same type of granules for all capsule strengths responds to an unmet medical need in paediatric patients and each dose is individually titrated based on the actively monitored individual clinical response. Altogether, Alkindi is considered to be approvable. The results of the **planned population PK analysis of study Infacort 003** will help to further refine the optimal dosing regimen for this replacement therapy which is available in a dose-appropriate form designed for children.

Conclusions

The overall B/R of Alkindi is positive.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Alkindi is favourable in the following indication:

Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years old).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0031/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.