CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213876Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	213876
Supporting document/s:	0001
Applicant's letter date:	11/29/2019
CDER stamp date:	11/29/2019
Product:	Alkindi®
Indication:	Pediatric Adrenal Insufficiency
Applicant:	Diurnal Limited
Review Division:	Division General Endocrinology
Reviewer:	Fred Alavi, PhD
Supervisor/Team Leader:	Todd Bourcier, PhD
Division Director:	Theresa Kehoe, MD
Project Manager:	Jennifer Johnson

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 213876 are owned by Diurnal Limited are data for which Diurnal Limited has obtained a written right of reference.
Any information or data necessary for approval of NDA 213876 that Diurnal Limited does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Diurnal Limited does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 213876.

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

A. Recommendation on approvability
Pharmacology/Toxicology recommends approval of Alkindi® Sprinkle (NDA 213876).

B. Recommendation - nonclinical safety assessment
Toxicology studies were not required based on the profile of the hydrocortisone drug substance and the components of the Alkindi drug product, and on the nonclinical information available from the reference listed drug, Cortef®.

1.1.2 Additional Nonclinical Recommendations: None

1.1.3 Labeling Recommended

(b) (4)

1.2 Brief Discussion of Nonclinical Safety Assessment

Alkindi® is a new pediatric-specific immediate release granulated hydrocortisone formulation in a capsule designed to meet the needs of pediatric patients with adrenal insufficiency. The hard-transparent capsules containing 0.5, 1.0, 2.0 or 5.0 mg of hydrocortisone granules are made to be opened and poured on the tongue or sprinkled on food. As a 505(b)(2) submission, the safety and efficacy of Alkindi® is based on previous FDA finding of safety and efficacy of Cortef® NDA 008697.

The quality attributes of the hydrocortisone drug substance did not identify any concerns that would require toxicological evaluation or invalidate reliance on the pharmacology and toxicology data available in the reference listed drug, Cortef®. Alkindi® contains multiple excipients, all of which have been used in other FDA approved products for pediatric and adult use at similar or higher concentrations, and do not raise toxicological concern. The hydrocortisone drug substance (with associated impurities) was produced consistent with USP and DMF monographs and does not raise toxicological concern. It is relevant to highlight that the available nonclinical toxicology studies with hydrocortisone were conducted in animal models without adrenal insufficiencies, and therefore risk is overestimated for patients with adrenal insufficiency, where the therapeutic goal is primarily restorative of cortisol activity.

2 Drug Information

2.1 Drug:

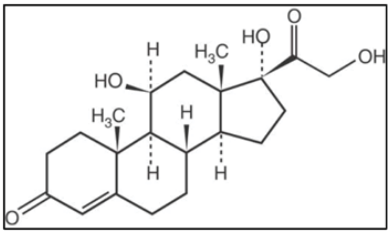
2.1.2 Generic Name: hydrocortisone

2.1.3 Drug Name: Alkindi® (also known as Infacort®)

2.1.4 Chemical Name: 11β,17α,21-trihydroxy-pregn-4-ene-3,20-dione

2.1.5 Molecular Formula/Molecular Weight: $C_{21}H_{30}O_5$, MW of 362.5 g/mol

2.1.6 Structure:



2.1.7 Pharmacologic class: Glucocorticoid Receptor Agonist (Replacement of Endogenous Cortisone)

2.2 Relevant INDs:

DMF (b) (4)
NDA 008697 (CORTEF®), NDA 009866 (SOLU-CORTEF®)

2.3 Clinical Formulation

(b) (4)

Single dose Alkindi® hard capsule for sprinkle "for opening" contain 0.5, 1.0, 2.0 or 5 mg of (b) (4) multiparticulate hydrocortisone.

2.3.1 Drug Formulation

(b) (4)

Alkindi® is an immediate release (b) (4) granulated hydrocortisone in a hard-transparent capsule. The active ingredient, hydrocortisone (b) (4) USP is covered by the referenced Drug Master File (b) (4) specification. The hard capsule will contain single dose of 0.5, 1.0, 2.0 and 5.0 mg of immediate release hydrocortisone granules.

The content of the capsule is poured on the tongue/spoon or sprinkled on food to facilitate oral administration of hydrocortisone to infants and children with adrenal insufficiency.

Qualitative and Quantitative Composition of Hydrocortisone Immediate Release Granules, Dose Strengths: 0.5mg, 1.0mg, 2.0mg and 5.0mg

(b) (4)

The excipients in the hydrocortisone immediate release granules have been used in oral pharmaceutical formulations.

The brief justification for each excipient is provided in the table below.

Shortlisted Excipients, their Function and Justification for Inclusion

Component	Function	Justification
(b) (4) (b) (4) Microcrystalline cellulose (b) (4)	(b) (4)	(b) (4)
(b) (4)		
Magnesium Stearate		
Hypromellose		
Ethyl cellulose		

2.3.2 Comments on Novel Excipients

There are no unique or novel excipients in Alkindi® formulation.

2.3.3 Comments on Impurities/Degradants of Concern

The drug substance characterization is well-defined, listed in the current US Pharmacopoeia (USP), and Diurnal has referenced the Drug Master File (b) (4) for Hydrocortisone (b) (4) The drug substance used to manufacture Alkindi® complies with the current USP monograph for hydrocortisone and with (b) (4) internal specification requirements.

Comments on Impurities/Degradants of Concern

The only degradation impurity that increased with accelerated storage of hydrocortisone at high temperature and humidity (40°C/75% Relative Humidity) was impurity (b) (4) which remained within the specification limit of (b) (4)% after 6-months. No new degradation products have been observed when drug product is stored at 30°C/75% RH or 25°C/60% RH.

(b) (4)

The impurities in the drug product correspond with impurity profile for hydrocortisone drug substance and complies with the USP monograph for hydrocortisone and refenced Cortef® NDA 008697.

Drug Product Release and Shelf life Specification for Hydrocortisone Immediate Release Granules in Capsules 0.5mg, 1.0mg, 2.0mg and 5.0mg

Test Method No.	Specification
Appearance (b) (4)	(b) (4)
Identification (HPLC) (b) (4)	
Identification (UV absorption) (b) (4)	
Assay (HPLC) (b) (4)	
Uniformity of dosage (b) (4)	
Delivered Assay (b) (4)	
Dissolution pH 1.2 (Release Characteristics) (b) (4)	
(b) (4)	
(b) (4)	
Purity (Impurities) (b) (4)	
Microbiology (b) (4)	
(b) (4)	(b) (4)

2.4 Proposed Clinical Population and Dosing Regimen

8 to 10 mg/m^2 /day, divided to 3 to 4 doses for adrenal insufficiency
10 to 15 mg/m^2 /day divided to 3 or 4 doses for congenital adrenal hyperplasia

2.5 Regulatory Background

Pre-IND application for Infacort® (Alkindi®) was submitted to the Division on March 25, 2015 by Coté Orphan on behalf of Diurnal Limited. The Division provided a Written Response on April 23, 2015 in which the Division agreed that based on the information available at that time, further toxicological evaluation of hydrocortisone is not necessary to support a 505(b) (2) marketing application for hydrocortisone. The sponsor was advised to refer to section 6.0 505(b)(2) Regulatory Pathway for additional information regarding 505(b)(2) submissions. The sponsor has referenced Cortef® NDA 008697.

4 Pharmacology

4.1 Primary Pharmacology

Hydrocortisone (cortisol) binds and activates cytosolic glucocorticoid receptor (GR). The newly formed receptor-ligand complex translocates to 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 (transactivation).
The activated hormone receptor interacts with specific transcription factors (such as AP-1 and NF-kB) and prevents the transcription of targeted genes. Glucocorticoids can 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 tumor necrosis factor alpha (TNFα) genes.

Notable physiological activities of cortisol/hydrocortisone:

- Glucose metabolism: Cortisol counteracts insulin and contributes to hyperglycemia by causing hepatic gluconeogenesis and inhibits the peripheral utilization of glucose (insulin resistance) by decreasing the translocation of glucose transporters (especially GLUT4) to the cell membrane. Cortisol also increases glycogen synthesis (glycogenesis) in the liver.
- Sodium: Cortisol inhibits sodium loss.
- Water: Cortisol acts as a diuretic hormone. Cortisol is essential for excreting a water load and adrenal insufficiency is associated with the clinical signs indicative of inappropriate antidiuretic hormone (ADH) secretion syndrome.
- Immune system: Cortisol can weaken the activity of the immune system. Cortisol prevents proliferation of T-cells by rendering the IL-2 producer T-cells unresponsive to IL-1, and unable to produce the T-cell growth factor. Cortisol also has a negative-feedback effect on IL-1. Natural killer cells are not affected by cortisol.
- Bone metabolism: Cortisol reduces bone formation, favoring long-term development of osteoporosis. Cortisol also reduces calcium absorption in the intestine.
- Blood pressure: Cortisol increases blood pressure by increasing the sensitivity of the vasculature to catecholamines; in the absence of cortisol, widespread vasodilatation occurs.

- Inflammation: Cortisol has anti-inflammatory properties, reducing histamine secretion and stabilizing lysosomal membranes, preventing their rupture and consequent damage to healthy tissues.

Drug activity related to proposed indication
Cortisol is an essential endogenous stress hormone released from the adrenal gland under the control of pituitary adrenocorticotropic hormone (ACTH) and deficiency results in adrenal crisis and death. Adrenal insufficiency (AI) results from either primary or secondary adrenal failure. Primary adrenal failure occurs when adrenal gland itself dysfunctions, resulting in either congenital (congenital adrenal hyperplasia, CAH), or acquired dysfunction (Addison's disease). Secondary AI occurs due to a lack of secretion of corticotropin-releasing hormone (CRH) from the hypothalamus or of ACTH from the pituitary, that leads to hypofunction of the adrenal cortex. In children, secondary AI is generally congenital thus require treatment from the time they are born. Hydrocortisone, the medicinal form of cortisol, is intended to normalize cortisol levels in children with adrenal insufficiency.

4.2 Secondary Pharmacology

Chronic exposure to excessive concentrations of endogenous cortisol or to pharmacological doses of glucocorticoids can elicit multiple deleterious effects on body structure and function. As noted earlier, corticosteroids can increase blood pressure by activation of the renin-angiotensin-aldosterone system. The renal effect (glomerular filtration rate, filtration fraction and renal blood flow) of corticosteroids has been well characterized in multiple species including humans.

4.3 Safety Pharmacology

No nonclinical safety pharmacology studies were provided by the sponsor for Infacort®. The safety profile of hydrocortisone has been well characterized. Substantially higher doses of hydrocortisone have been used as an immunosuppressant and anti-inflammatory agent in humans than those proposed for pediatric subjects with adrenal insufficiency (hormone replacement).

Administration of 8.5 mg/kg hydrocortisone twice daily for 84 days to Beagle dogs increased arterial blood pressure; however, the rise was only significant from Day 28 forward and no study dog developed blood pressure to the point of hypertension (defined as > 160 mmHg). Hydrocortisone increased urinary protein excretion in treated dogs. The increase in proteinuria was thought to be primarily of glomerular origin considering only albuminuria was identified by electrophoresis. The investigators hypothesized that the increase in glomerular filtration rate and renal blood flow were the most likely causes of proteinuria. Both the rise in blood pressure

and proteinuria were reversible and completely restored within 1 month after cessation of hydrocortisone administration.

5 Pharmacokinetics/ADME/Toxicokinetics

Nonclinical pharmacokinetic bridging studies have not been conducted for Alkindi®. Hydrocortisone has high permeability through the intestinal membrane, therefore absorption is limited by the dissolution rate, GI content and bile acids. Over 90% of cortisol and the metabolites of cortisol are conjugated in the liver and excreted in the urine. Very little cortisol is excreted in the urine unchanged (< 1%). In circulation, cortisol is bound (70 to 90%) to corticosteroid binding globulin (CBG, transcortin) and to a small extent to albumin. Since only the free fraction (5% to 10%) is active and CBG is a high affinity low capacity cortisol binding protein, significant increase in cortisol levels (treatment) beyond the binding capacity is expected to result in greater free cortisol fraction in the circulation. In comparison, albumin is high capacity low affinity, making CBG's role more consequential in regulating free cortisol levels.

6 General Toxicology

Dedicated acute and repeat-dose nonclinical toxicity studies of Infacort® have not been conducted. There is extensive human and animal experience with hydrocortisone. Oral administration of hydrocortisone (Alkindi®) is expected to normalize the endogenous levels of the stress hormone. Furthermore, chronic administration of high doses is generally associated with hypertension, immune suppression, glucose and insulin dysregulation, and osteoporosis in non-deficient subjects.

Acute Toxicology
Administered hydrocortisone to rats either intraperitoneally (acute LD50: 150 mg/kg) or subcutaneously (acute LD50 > 1800 mg/kg) elicited a high rate of mortality by Week 2 (due to infections) and was likely driven by the immunosuppressive properties of hydrocortisone. Additional effects observed during studies in rats and mice included a notable reduction in adrenal weights, liver damage, lung consolidation (swelling or a hardening of the soft lung tissue) and gastrointestinal changes.

Acute toxicity data for hydrocortisone aceponate, an ester of hydrocortisone, (a component of the veterinary pharmaceutical product (Easotic) designed to treat dogs that suffer from ear infections) indicates that this compound induces a variety of toxicity symptoms including sedation, ataxia, dyspnea, cyanosis, mydriasis, lachrymal secretion, muscular hypotonia, decreased food consumption and decreased body weight gain, vomiting and death. However, following oral administration of hydrocortisone aceponate, no acute toxic effects were observed at 1000 mg/kg in rats and mice or at 8000 mg/kg in dogs. Following intraperitoneal administration, no acute toxic effects were noted at 464 mg/kg in rats and mice, or at 100 mg/kg in dogs.

Repeat-Dose Toxicology
The effects of chronic low dose hydrocortisone administration on liver lipids and plasma lipids were assessed in male Wistar rats. Over a period of 6 months, rats were fed daily with a controlled diet and the experimental group ingested a hydrocortisone solution at 0.5 mg/kg, while the control group consumed a comparable volume of water. Long-term intake of hydrocortisone significantly affected liver phospholipid distribution and fatty acid composition. The percentage of phosphatidylethanolamine was lower in the hydrocortisone group, while the percentages of sphingomyelin and phosphatidylserine were higher. Decreased levels of cholesterol and LDL-cholesterol were also found in the plasma of the hydrocortisone-treated rats.

7 Genetic Toxicology

The genotoxic potential of Infacort® has not been assessed by the Sponsor and conflicting genotoxic evaluations of hydrocortisone have been reported in the literature. Hydrocortisone was negative in an Ames assay (± S9) but positive or equivocal in the chromosomal aberration test in human lymphocytes, the mouse micronucleus test, and an in vivo evaluation of sister chromatid exchanges. No purity data was reported for these assays, and they were not GLP compliant. Genotoxicity studies (GLP-compliant) were conducted for the EMA approval of the veterinary pharmaceutical Easotic® (hydrocortisone aceponate) and did not reveal evidence of mutagenicity or clastogenicity.

8 Carcinogenicity

The carcinogenic potential of Infacort® has not been assessed by the sponsor.
A study conducted in 1976 showed no carcinogenic potential in rats administered doses of 5.36 mg/kg/day (5 days/week) via oral dosing (Schmäl D, Habs M., 1976).
.

9 Reproductive and Developmental Toxicology

The reproductive and developmental toxicology of Infacort® has not been assessed by the Sponsor. Extensive data in the literature indicate that hydrocortisone is teratogenic and embryotoxic in animal models, especially at high doses. In rodents exposed during organogenesis, there were multiple malformations, including cleft palates, and in rabbits there was an increase in polycystic kidney disease. Segment III studies indicated that maternal treatment can lead to alterations of hormone homeostasis and reproductive performance in adult offspring. Of note, these studies were conducted in animals with normal adrenal function and therefore are more reflective of potential adverse outcomes from exposure to excessive levels of hydrocortisone.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FRED K ALAVI
08/28/2020 12:43:15 PM
Nonclinical recommends Alkindi approval.

TODD M BOURCIER
08/28/2020 01:04:26 PM
I concur