

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213876Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	9/25/2020
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 213876
Applicant	Diurnal
Date of Submission	11/29/2019
PDUFA Goal Date	9/29/2020
Proprietary Name	Alkindi Sprinkle granules
Established or Proper Name	Hydrocortisone
Dosage Form(s)	0.5 mg, 1 mg, 2 mg and 5 mg, oral granules
Applicant Proposed Indication(s)/Population(s)	Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 17 years old)
Applicant Proposed Dosing Regimen(s)	Starting doses are 8-10 mg/m ² /day for patients with adrenal insufficiency alone and 10-15 mg/m ² /day in patients with congenital adrenal hyperplasia administered in three or four divided doses
Recommendation on Regulatory Action	<i>Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	Replacement therapy in pediatric patients with adrenocortical insufficiency
Recommended Dosing Regimen(s) (if applicable)	Starting dose is 8-10 mg/m ² /day in all types of adrenal insufficiency.

Material Reviewed/Consulted	Names of discipline reviewers
Medical Officer Review	William Lubas
Pharmacology Toxicology Review	Fred Alavi, Todd Bourcier
OPQ Review	Ali Mohammadi, David Claffey, Kejun Cheng, Aditi Thakur, Debasis Ghosh, Min Li, Leeza Rahimi, Hamet Toure, Dhanalakshmi Kasi Daniel Jansen, Su (Suong) Tran
Clinical Pharmacology Review	Mohammad (Abir) Absar, Jayabharathi Vaidyanathan
OPDP	Ankur Kalola, Melinda McLawhorn
OSE/DMEPA	Melina Fanari, Sevan Kolejian
OSE/DPV	Amy Chen, Christian Cao
DPMH	Wenjie Sun, Miriam Dinatale

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DPV= Division of Pharmacovigilance

DPMH=Division of Pediatric and Maternal Health

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

On 11/29/2019 Diurnal submitted this 505(b)(2) new drug application (NDA) for hydrocortisone oral granules (refer to as hydrocortisone granules hereafter) seeking approval for the following indication:

Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 17 years old).

Hydrocortisone is a corticosteroid with predominant glucocorticoid activity. Hydrocortisone granules is a new pediatric-specific presentation of hydrocortisone that is supplied as granules packed in capsule. The capsule should be opened to sprinkle granules over the food or to administer them directly into the mouth. The proposed dose strengths are 0.5, 1.2 and 5 mg.

The Applicant relies on FDA's previous findings of safety and effectiveness for the reference drug, Cortef Tablets (hydrocortisone; refer to as Cortef hereafter; NDA 008697) that is also approved for the treatment of adrenocortical insufficiency (adrenal insufficiency).¹

Adrenal insufficiency (adrenocortical insufficiency; AI) is characterized by decreased production of glucocorticoids and in some cases, mineralocorticoids. AI is a severe and potentially life-threatening condition due to the central role of these hormones in energy, salt and fluid homeostasis. AI can be divided into two types, primary or central. Primary AI is due to the failure of adrenal gland to produce glucocorticoids; the causes of primary adrenal gland failure may be acquired (e.g., infection, hemorrhage) or congenital due to the defects in cortisol synthesis (e.g., congenital adrenal hyperplasia). Central AI is due to decreased adrenocorticotropic hormone (ACTH) secretion by pituitary gland leading to the insufficient glucocorticoid production by adrenal glands. Congenital adrenal hyperplasia (CAH), which occurs in approximately 1 of 14,200 live births, is the most common cause of primary adrenal insufficiency in children (75% of cases).² Central adrenal insufficiency may be due to congenital defects relating to the normal development of the hypothalamus and/or pituitary, or to the acquired injury to these structures by trauma, neoplasm, surgery or cranial irradiation. Clinical manifestations of AI in children are nonspecific and may include poor feeding, weight loss, diarrhea, hypovolemia, hypoglycemia, muscle hypotonia. In its most severe presentation, adrenal insufficiency may result in adrenal crisis leading to hypotension, electrolyte abnormalities, circulatory collapse and death.

The current standard treatment of AI consists of the physiologic replacement with corticosteroids. Current treatment guidelines for adrenal insufficiency (Endocrine Society, 2016) recommend using hydrocortisone as the first line of therapy in adults and children with AI.³ The recommended starting doses of hydrocortisone in children with AI is 8-10 mg/m² administered in three or four divided doses. In general, hormonal monitoring of corticosteroid replacement is not recommended, and the adjustment of doses is based on clinical response and the avoidance of the signs of over and/or under replacement. Corticosteroid dosing must be increased during times of stress.

There are multiple oral hydrocortisone products (Cortef and generic products) approved for the replacement therapy in adult and pediatric populations with AI and are available in tablets 5 mg, 10 mg and 15 mg. Pediatric patients usually require smaller than available unit doses, so the tablets are crushed by parents that may result in the administration of incorrect dose and adverse

¹ <https://dailymed.nlm.nih.gov>

² Perry R, Kecha O, Paquette J, Huot C, Van Vliet G, Deal C. Primary adrenal insufficiency in children: twenty years experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab.* 2005;90(6):3243.

³ Stefan R, Bornstein, Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016; 101 (2): 364–389

events associated with over or undereplacement. Adverse events associated with under-replacement include fatigue, malaise, and/or other signs and symptoms of AI. The use of excessive doses of corticosteroids may lead to glucose intolerance, hypertension, weight gain, suppression of growth and short adult height, increased risk of infections, osteoporosis, etc. Both conditions may lead to increased morbidity and mortality. Thus, the expected advantage of hydrocortisone granules compared to tablet formulations of hydrocortisone is the availability of smaller doses and more accurate dosing in pediatric patients with AI.

Benefits

The evidence provided in this application are sufficient to supports the approval of hydrocortisone granules for the replacement therapy in children with AI indication. Cortef was previously determined to be safe and effective for the same indication, i.e. treatment of AI in all patients including pediatric patients with AI. The Applicant satisfactory established a scientific bridge allowing reliance on FDA's finding of safety and effectiveness for Cortef to support approval of hydrocortisone granules for the treatment of pediatric AI. A pivotal, open-label, randomized, single-dose, two period, crossover relative bioavailability study of hydrocortisone granules versus Cortef in dexamethasone-suppressed healthy adult volunteers in the fasted and fed states (study 007) demonstrated that pharmacokinetic (PK) characteristics of hydrocortisone granules are bioequivalent to the reference drug, Cortef to justify reliance on the listed drug: the 90% confidence interval of geometric mean ratio (GMR) for C_{max} , AUC_t and AUC_{inf} of serum cortisol were within the pre-specified acceptance criteria of 80 to 125% under both fasting and fed condition. Thus, it is expected that the benefits of hydrocortisone granules use in the intended population will be similar to the benefits of the reference drug, Cortef. In addition, data from pivotal and supportive PK study 006 demonstrated that systemic exposure to hydrocortisone granules was not affected by food. Thus, the administration of drug with soft food or yogurt is acceptable. Lastly, the data obtained from two pediatric studies in subjects with AI <6 years old: 003 (single dose study) and 004 (long-term safety study) provide supportive evidence for the use of hydrocortisone granules as replacement therapy in pediatric patients with AI. The PK data obtained from a single dose study 003 demonstrated that hydrocortisone was sufficiently absorbed from hydrocortisone granules to rise serum cortisol levels: serum cortisol levels were > 27 mcg/dl (normal levels that exclude AI) at 60 minutes in all subjects. The data from long-term (2.5 years) single arm study using hydrocortisone granules in children with AI further supports the conclusion that hydrocortisone granules sufficiently replaces missing corticosteroids when administered as directed in children with AI; no events of adrenal insufficiency was reported in this study. Lastly, based on population PK analysis (using the adult PK data to model dosing and compare drug elimination characteristics in children of all ages (0-18 years), the PK in older children, 6-17 years old is not expected to be different as compared to adults or to children < 6 years old.

Risks

As stated above, the Applicant satisfactory established a scientific bridge allowing reliance on FDA's finding of safety for Cortef to support approval of hydrocortisone granules for the treatment of pediatric AI. Thus, it is expected that the risks of hydrocortisone granules use in replacement doses will be similar to the risks of reference drug, Cortef in pediatric patients with AI. The risks associated with use of corticosteroids including hydrocortisone are well recognized. In general, these risks are associated with under-replacement or overreplacement. These risks are dose- and time dependent. This risk of undereplacement is associated with signs and symptoms of AI. The most common adverse reactions associated with overtreatment are suppressed growth, cushingoid appearance, hyperglycemia, risk of infection.

Additional supportive safety data obtained from the Applicant's clinical program demonstrated that hydrocortisone granules was well tolerated by healthy adults and children with AI. No new safety signals associated with hydrocortisone use were identified in these studies. No adverse reactions of AI or adverse events associated with use of corticosteroids in supraphysiologic doses (e.g., growth suppression, weight gain, hyperglycemia) were reported in children with AI treated with Hydrocortisone granules for up to 2.5 years. Overall, the risks of under-replacement can be mitigated by monitoring for the signs and symptoms of adrenal insufficiency during the treatment and adjustment of the doses, and by increasing dose during events required higher doses of corticosteroids (e.g., acute illness, surgery, trauma). Monitoring for these adverse reactions and use of the lowest effective dose mitigate the risks of over-replacement.

The potential formulation-specific (i.e. granules packed in capsule) risks are choking if the capsule is swallowed as whole and/or risk of underdosing. The underdosing and consequent adrenal insufficiency is not expected if capsule is accidentally swallowed as whole based on in vitro dissolution profile of the drug: the systemic exposure from the administration of intact capsule if swallowed as whole is expected to be similar to the systemic exposure from the administration of granules. These data were found to be sufficient and no further in-vivo studies were required. No choking events was reported to date in Applicant's clinical program. These risks can be mitigated by proper labeling that include the clear instruction on the drug administration (e.g., do not swallow the capsule") and indicating that the capsule should not be swallowed as whole.

In conclusion, the evidence provided in this application is sufficient to support the approval of hydrocortisone granules for the cortisol replacement therapy in children with AI indication. The Applicant satisfactory established a scientific bridge allowing reliance on FDA's finding of safety and effectiveness for Cortef that is approved as a replacement therapy in patients with AI. Thus, it is expected that the benefits and risks of hydrocortisone granules use will be similar to the benefits and risks of reference drug, Cortef, in pediatric patients with AI. The expected class effects will be mitigated through the labeling. The benefit of the proposed hydrocortisone formulation to allow for more accurate dosing in children outweighs the theoretical formulation-specific risk of choking if capsule is swallowed as whole. This risk can be mitigated through the appropriate labeling and enhanced pharmacovigilance. Thus, I recommend approval of hydrocortisone granules for the proposed indication. However, I do not recommend specifying the types of AI in the indication (primary, secondary, CAH). Adrenal insufficiency is a recognized disease that is associated with decreased corticosteroid production by adrenal gland regardless of the cause (hemorrhage, trauma, surgery, infection, CAH, etc.) or type (primary, secondary, tertiary). Thus, the efficacy and safety of hydrocortisone replacement therapy is expected to be the same in all types of AI. In addition, I do not recommend approval of the separate higher starting doses of 10-15 mg/m² for the treatment of AI in subpopulation of patients with CAH in the label. These doses are higher than required for the replacement therapy and are used to suppress adrenal sex steroids in order to treat symptoms of CAH associated with elevated adrenal sex steroids. Since the proposed indication for hydrocortisone granules is the treatment of adrenal insufficiency only, the lower replacement doses are sufficient to treat and prevent signs and symptoms of adrenal insufficiency of all types. I also recommend administration of Hydrocortisone granules in 2-3 divided doses. Such a regimen mimics the normal circadian rhythm of cortisol with peak levels in early morning and undetectable levels at midnight. The Applicant's proposed regimen of the drug administration 4 times a day is non-physiologic and may be associated with overreplacement.^{4 5}

⁴ Weitzman E.D., Fukushima D., Nogeire C., Roffwarg H., Gallagher T.F., Hellman L. (1971). Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab* 33: 14-22

⁵ Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. *J Pediatr*. 1990 Dec;117(6):892-6

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • AI is a serious disease characterized by decreased production of corticosteroids regardless of type and etiology of the disease (primary, secondary, due to CAH, infection, etc.). • CAH is the most common cause of primary adrenal insufficiency in children (75% of cases).⁶ • Clinical manifestations of AI are the same regardless of type of AI or age of patients. The symptoms include weight loss, diarrhea, hypovolemia, hypoglycemia, muscle hypotonia. • AI is a severe and potentially life-threatening condition. Adrenal crisis may lead to hypotension, electrolyte abnormalities, circulatory collapse and death. • The current standard treatment of AI is the same in all types of AI and consists of the physiologic replacement with corticosteroids. 	<ul style="list-style-type: none"> • AI is a serious and potentially life-threatening disease. • In its most severe presentation, adrenal insufficiency may result in adrenal crisis leading to hypotension, electrolyte abnormalities, circulatory collapse and death. • Replacement therapy with corticosteroids is crucial in management of patients with all types of AI to prevent morbidity and mortality.
Current Treatment Options	<ul style="list-style-type: none"> • Hydrocortisone is the first line of therapy in adults and children with AI.⁷ • The recommended starting dose of hydrocortisone in children is 8-10 mg/m² administered in three or four divided doses. • Hormonal monitoring of corticosteroid replacement is not recommended, and the adjustment of doses is based on clinical response and the avoidance of the signs of over and/or under replacement. • Multiple oral hydrocortisone products (Cortef Tablets and generic products) approved for the replacement therapy in adult and pediatric populations with AI and are on US market. All oral hydrocortisone products are available as tablets in strengths 5 mg, 10 mg and 20 mg. 	<ul style="list-style-type: none"> • The goal of treatment is to improve clinical signs and symptoms of the disease and to prevent adrenal crisis. • Hydrocortisone is the first line of therapy in children with AI • Approved oral hydrocortisone formulations are 5 mg, 10 mg and 15 mg tablets. • Children require smaller than available unit doses, thus, the tablets are crushed by parents that may result in the administration of incorrect dose and adverse events associated with over- or under-replacement • The expected advantage of hydrocortisone granules in capsule compared to a solid oral formulation of hydrocortisone in children with AI is the administration of more precise doses.

⁶ Perry R, Kecha O, Paquette J, Huot C, Van Vliet G, Deal C. Primary adrenal insufficiency in children: twenty years experience at the Sainte-Justine Hospital, Montreal. J Clin Endocrinol Metab. 2005;90(6):3243.

⁷ Stefan R. Bornstein, Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2016; 101 (2): 364–389

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> • Cortef (NDA 008697) is approved for the treatment of AI in adult and pediatric patients. • The Applicant has established a scientific bridge allowing reliance on FDA’s finding of safety and effectiveness for Cortef to support approval of hydrocortisone granules for the treatment of AI in pediatric patients (Study 007). The data demonstrated that PK of hydrocortisone granules is bioequivalent to the reference drug, Cortef: the 90% confidence interval of geometric mean ratio (GMR) for C_{max}, AUC_t and AUC_{inf} of serum cortisol were within the pre-specified acceptance criteria of 80 to 125% under both fasting and fed condition. • The data from PK studies 006 and 007 demonstrated that that systemic exposure to hydrocortisone granules is not affected by food. • No well-controlled studies were conducted or required to establish the efficacy of the drug for the proposed indication. However, the supportive PK data obtained from pediatric single dose study 003 provided additional evidence that hydrocortisone is sufficiently absorbed from hydrocortisone granules when the drug is administered as directed: the serum cortisol levels increased to > 27 mcg/dl (normal levels) at 60 minutes in all subjects. In addition, no events of AI were reported in children treated with hydrocortisone granules for up to 2.5 years in study 004. • Population PK analysis (using the adult PK data to model dosing and compare drug elimination characteristics in children of all ages (0-18 years)) demonstrated that PK in older children, 6-17 years old is similar to PK of hydrocortisone in adults and children < 6 years old. 	<ul style="list-style-type: none"> • The Applicant satisfactory established a scientific bridge allowing reliance on FDA’s finding of safety and effectiveness for Cortef to support approval of hydrocortisone granules for the treatment of pediatric AI. • Thus, the benefits and risks hydrocortisone granules as replacement therapy is the similar to the benefits and risks of reference drug, Cortef in pediatric patients with AI. • PK profile of hydrocortisone is not affected by food and the drug can be administered with soft food. • PK characteristics of hydrocortisone granules in older children are the same as in adults and children < 6 years old based on PopK analysis • The data from long-term study 004 supports the conclusion that use of hydrocortisone granules for up to 2.5 years prevents signs and symptoms of AI when the drug is administered as directed (i.e., sprinkled on the tongue, mixed with yogurt, etc.).
Risk and Risk Management	<ul style="list-style-type: none"> • The Applicant has established a scientific bridge allowing reliance on FDA’s finding of safety for Cortef Tablets for the proposed indication. • Safety profile of hydrocortisone is well established and consistent with the safety profile for the corticosteroid class drugs. • Adverse reactions associated with use of corticosteroid products is in general due to under or overreplacement. <ul style="list-style-type: none"> - Adverse events associated with underreplacement include fatigue, malaise, or other signs and symptoms of AI. - The use of excessive doses of corticosteroids may lead to glucose intolerance, hypertension, weight gain, suppression of growth and short adult height, increased risk of infections, osteoporosis, etc. • Supportive data from the Applicant’s clinical studies did not identify new hydrocortisone-specific safety signals. • The potential formulation-specific risks are underdosing and/or choking if the capsule is accidentally administered as whole. <ul style="list-style-type: none"> - No underdosing is expected based on the drug dissolution profile: the systemic exposure from the administration of intact capsule if 	<ul style="list-style-type: none"> • Safety profile of hydrocortisone granules in patients with AI is expected to be similar to Cortef safety profile. • The major risks associated with use of corticosteroids are hypersensitivity, cataract, adrenal insufficiency, Cushing’s Syndrome, weight gain, delayed growth, hyperglycemia, risk of infection. • Safety information for this product will be adequately communicated in product labeling and will be mitigated by the use of the lowest effective doses. No REMS or Post-Marketing Requirements are necessary. • The potential risk of choking associated with incorrect drug administration (i.e. when capsule is swallowed as whole) will be mitigated by proper administration instructions in

Cross Discipline Team Leader Review

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>swallowed as whole will be similar to the systemic exposure from the administration of granules.</p> <ul style="list-style-type: none"> - No choking events were reported in Applicant's studies. This risk can be mitigated by proper labeling and clear administration instructions to indicate that the capsule should not be swallowed. 	<p>the label. The post-marketing reports for medication errors will be monitored through enhanced pharmacovigilance and this issue will be revisited if the need arises.</p>

2. Background

On 11/29/2019 Diurnal submitted a New Drug Application (NDA) for hydrocortisone oral granules formulation (refer to as hydrocortisone granules hereafter) under Section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act in support of the following indication:

Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 17 years old).

The Applicant relies on FDA's previous findings of safety and effectiveness for the reference drug, Cortef (hydrocortisone) Tablets (refer to as Cortef hereafter; NDA 008697) as permitted under 505(b)(2). Cortef is approved for the treatment of adrenal insufficiency (AI) and for the treatment of other endocrine (e.g., congenital adrenal hyperplasia, non-suppurative thyroiditis) and non-endocrine conditions (e.g., rheumatic, collagen, dermatologic, allergic disorders) in adult and pediatric patients (refer to Cortef label for the full list of the approved indications⁸). Cortef is available in the following strengths: 5 mg, 10 mg, and 20 mg. The approved doses of Cortef are not condition-specific and/or age-specific. As per label, "the initial dosage of CORTEF Tablets may vary from 20 mg to 240 mg of hydrocortisone per day depending on the specific disease entity being treated...; dosage requirements are variable and must be individualized on the basis of the disease under treatment and the response of the patient"⁸.

Hydrocortisone granules is a new pediatric-specific presentation of hydrocortisone. Hydrocortisone (cortisol) is a corticosteroid with predominant glucocorticoid activity. Hydrocortisone granules is supplied as granules packed in capsules. The capsules have to be opened to sprinkle granules over the food or to administer them directly into the mouth. The proposed strengths are 0.5, 1.2 and 5 mg. The proposed doses are 8-10 mg/m²/day in patients with adrenal insufficiency and 10-15 mg/m²/day in patients with adrenal insufficiency secondary to congenital adrenal hyperplasia (CAH) administered in three or four divided doses.

AI is characterized by decreased production of corticosteroids (glucocorticoids and/or mineralocorticoids). AI can be divided into two types, primary (due to the failure of adrenal gland) or central (due to the decreased adrenocorticotrophic hormone (ACTH) secretion by pituitary gland or corticotropin-releasing hormone (CRH) from the hypothalamus).

AI may occur in all age groups, including neonates. Congenital adrenal insufficiency (CAH), which occurs in approximately 1 of 14,200 live births, is the most common cause of primary

⁸ <https://dailymed.nlm.nih.gov>

adrenal insufficiency in children (75% of cases).⁹ CAH is a group of autosomal recessive disorders characterized by impaired cortisol synthesis. The cortisol synthetic block leads to accumulation of cortisol precursors that are diverted to increased sex hormone biosynthesis. Thus, the symptoms of CAH include the symptoms of adrenal insufficiency (due to decreased cortisol synthesis) and symptoms of virilization, rapid growth and precocious puberty (caused by increased sex steroid levels).

AI is a severe and potentially life-threatening condition due to the central role of corticosteroids in energy, salt and fluid homeostasis. Most symptoms of AI are nonspecific and include weakness, fatigue, musculoskeletal pain, weight loss, abdominal pain, depression, anxiety, orthostatic hypotension, changes in blood count (anemia, eosinophilia, lymphocytosis), hypoglycemia, etc. In its most severe presentation, AI may result in adrenal crisis leading to hypotension, electrolyte abnormalities, circulatory collapse and death. Adrenal crisis can be observed as the initial presentation of adrenal insufficiency or as the result of inadequate replacement therapy or inadequate stress coverage with corticosteroids in patients with known adrenal insufficiency.

The current standard treatment of AI consists of the physiologic replacement with corticosteroids regardless of the cause of the disease or type of AI (primary or secondary); mineralocorticoid replacement is required in patients with primary AI. Current treatment guidelines for adrenal insufficiency (Endocrine Society, 2016) recommend using hydrocortisone as the first line of therapy in adults and children with AI, although other corticosteroids can be used as well (e.g., prednisone)¹⁰. The overall goal of treatment is to improve clinical signs and symptoms of the disease including body weight, blood pressure, energy levels and growth velocity in children. Hormonal monitoring of corticosteroid replacement is not recommended, and the adjustment of doses is based on clinical response and the avoidance of the signs of over and/or under replacement. Corticosteroid dosing must be increased during times of stress.

Several oral corticosteroid products with glucocorticoid activity (e.g., hydrocortisone (Cortef and generic formulations), prednisone, dexamethasone) for the replacement therapy in pediatric and adult patients with AI are approved and on US market. Adverse reaction profile of these products is similar and is usually associated with under- or over-replacement. Adverse events associated with under-replacement include fatigue, malaise and other signs and symptoms of AI. The use of excessive doses of corticosteroids may lead to glucose intolerance, hypertension, weight gain, suppression of growth and short adult height (in children), increased risk of

⁹ Perry R, Kecha O, Paquette J, Huot C, Van Vliet G, Deal C. Primary adrenal insufficiency in children: twenty years experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab.* 2005;90(6):3243.

¹⁰ Stefan R, Bornstein, Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016; 101 (2): 364–389

infections osteoporosis, etc.). Both conditions may lead to increased morbidity and mortality. Thus, all corticosteroids labels emphasize that doses should be individualized based on patient clinical signs and symptoms and lowest effective dose should be used.

Hydrocortisone is the drug of choice in pediatric patients with AI because of its short half-life and titration schedule based on the size of the growing child allowing to achieve the lowest effective dose. The use of long-acting potent corticosteroids (prednisone, dexamethasone) is not recommended for the treatment of AI in children due the high risk of growth suppression. In children, the recommended starting dose is 8-10 mg/m² administered in three or four divided doses to mimic physiologic circadian rhythm of cortisol.^{11 12} The doses of corticosteroids used in patients with CAH are in general higher (10-15 mg/m²) than physiologic replacement doses required to adequately treat all types of adrenal insufficiency, since the goal of CAH treatment not only to replace corticosteroids, but also to suppress the excessive ACTH-stimulated production of the adrenal androgens to reduce symptoms of virilization and precocious puberty¹³. Currently, all oral hydrocortisone products are available as tablets in strengths 5 mg, 10 mg and 20 mg. However, younger patients (including neonates) usually require smaller than available unit doses. In order to administer lower doses, the tablets are crushed by parents. This may result in the administration of incorrect dose and over or underreplacement. Thus, the expected advantage of hydrocortisone granules compared to a solid oral formulation of hydrocortisone is the availability of smaller doses and ease of administration in children.

Regulatory background

Cortef was approved in 1952 for the treatment of adrenal insufficiency (NDA 008697). Based on drug efficacy study implementation (DESI) review by the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, the effectiveness of Cortef for the treatment of adrenal insufficiency was established in 1970.¹⁴

Hydrocortisone granules Regulatory history

Hydrocortisone granules is being developed for the replacement therapy in pediatric patients with AI of all types. The Applicant indicated that hydrocortisone granules is not developed for

¹¹ Stefan R. Bornstein, Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 2016; 101 (2): 364–389

¹² Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. *J Pediatr*. 1990 Dec;117(6):892-6. doi: 10.1016/s0022-3476(05)80128-3.

¹³ Phyllis W. Speiser, Wiebke Arlt, Richard J. Auchus, Laurence S. Baskin, Gerard S. Conway, Deborah P. Merke, Heino F. L. Meyer-Bahlburg, Walter L. Miller, M. Hassan Murad, Sharon E. Oberfield, and Perrin C. White. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 2018; 103 :1-46

the treatment of adrenal insufficiency in adults because there are “licensed hydrocortisone products available for use in adults” (refer to Type C meeting minutes in DARRTS from 2/6/2019). Indeed, there are multiple hydrocortisone and other corticosteroid products approved for the treatment of AI. The strength of the approved hydrocortisone tablets for the treatment of AI in adults is 5 mg, 10 mg and 20 mg and is within the dose range required for the treatment of adult AI. In addition, the proposed strength of hydrocortisone granules is small and will require the administration of multiple capsules to achieve the recommended adult dose that may lead to medication errors and/or decrease compliance.

- Pre-IND meeting (5/22/2015)

This meeting set the overall direction of the hydrocortisone granules development program. FDA provided the guidance on submission of 505(b)(2) NDA and on the CMC information to be included in IND. FDA also agreed that further toxicological evaluation of hydrocortisone granules is not necessary to support the proposed 505(b)(2) application and that the adequacy of data that bridges the differences between the Sponsor’s drug and the currently approved hydrocortisone formulation will be reviewed upon NDA submission. FDA recommended to include pharmacokinetic (PK) endpoints (e.g., AUC, C_{max} and C_{trough}) for cortisol in Phase 3 trial (003) evaluating the use of the hydrocortisone granules in children with AI. Lastly, FDA recommended to conduct a food effect study, since the younger children are unable to swallow the granules and may require mixing of the drug with food.

- The drug received orphan designation status for the treatment of pediatric AI in May 2015 by the Office of Orphan Products Development

- IND 123322 for hydrocortisone granules was opened on 10/31/2017 with a protocol for an open label, randomized, single dose, two-period cross over relative bioavailability study of Infacort (hydrocortisone granules) versus Cortef immediate release hydrocortisone tables in dexamethasone suppressed healthy adults (study 007). The Sponsor was allowed to proceed with this study.

- Hydrocortisone granules were granted a marketing authorization by the European Commission in February 2018 under the proprietary name Alkindi in doses of 0.5, 1, 2 and 5 mg for a similar indication, i.e. “replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years of age)”.

- Type C meeting (2/6/2019)

During this meeting, the content and format of planned NDA was discussed and agreed upon. FDA asked the Sponsor to clarify the overall plan for the submission of NDA, proposed indication and intended population. The Sponsor confirmed that the plan was to submit 505(b)(2) application relying on reference drug, Cortef. The published literature will

be submitted to “provide additional support”. The Sponsor also clarified that the intended population is pediatric patients with AI and that the drug is not developed for the adults with AI for the reasons stated above. Lastly, the Sponsor confirmed that the only indication they are seeking at this time is replacement therapy of adrenal insufficiency in pediatric patients.

The risks associated with swallowing the capsule as whole (e.g., choking or inappropriate dose delivery) were also discussed during the meeting. The Sponsor indicated that there were no reports of choking with their drug in the completed studies and there were no postmarketing choking reports since the product was approved in Europe. The Sponsor also indicated that they will provide in NDA the in vitro dissolution profile to justify that the capsule products if swallowed as whole behaves as an immediate-release product. (b) (4)

FDA

requested that the Sponsor submitted the additional data that the proposed product user interface supports the safe use of the product. Lastly, FDA requested that the Sponsor to include all postmarketing data on choking risk since the date of the drug approval in Europe in NDA submission.

- The content of planned NDA was further clarified on 7/1/2019. FDA confirmed that the tabular format of a summary of the information to be included in the Summary of Clinical Efficacy and Summary of Clinical Safety sections of NDA is acceptable.
- The Sponsor and FDA further discussed the requirements for human factor study on multiple occasions due to the safety concerns discussed above (swallowing of capsule as whole and/or choking). Division of Medication Error Prevention and Analysis (DMEPA) reviewed all available information submitted by the Sponsor and concluded that these risks do not represent new or unique risks as compared to other similar products. Therefore, DMEPA determined that it is not required for the Sponsor to submit the results from a human factor study to support their marketing application (refer to FDA’s Advice Letter from 8/22/2019).
- NDA submission: 2/26/2016.
- FDA asked the Applicant to clarify whether they were seeking “one indication, treatment of adrenal insufficiency only (including adrenal insufficiency in congenital adrenal hyperplasia), or two separate indications, (1) treatment of adrenal insufficiency and (2) treatment of congenital adrenal hyperplasia” (refer to FDA’s Letter from 2/11/2020). The Applicant responded on 3/11/2020 and reiterated that the only proposed indication is “replacement therapy of adrenal insufficiency (AI) (including

adrenal insufficiency in congenital adrenal hyperplasia), in infants, children and adolescents (from birth to <17 years old)".

3. Product Quality

The review team from Office of Pharmaceutical Quality (OPQ) recommend approval of this application (refer to OPQ executive summary from 8/28/2020). The Office of Pharmaceutical Quality and Office of Compliance has determined the manufacturing facilities are acceptable.

All CMC information is obtained from Drug Master File (DMF) (b) (4). The Applicant obtained right of reference to NDA 008697 (Cortef Tablets) and to the relevant DMF (b) (4) for all CMC information on the drug substance and drug product. This information was reviewed and found to be acceptable.

The active pharmaceutical ingredient (API), hydrocortisone (b) (4) the United States Pharmacopeia (USP) used in hydrocortisone granules has a molecular weight of 362.5. The API is a Biopharmaceutical Classification System (BCS) I compound with a high solubility and permeability. (b) (4)

Hydrocortisone granules is manufactured as hydrocortisone immediate-release multi-particulate granules at strengths of 0.5 mg, 1 mg, 2 mg or 5 mg and are supplied in hard transparent capsule. The hard capsule is a container only and must not be swallowed. The capsules have color-coded imprint for each strength. The identification of each strength was found to be adequate by the reviewers. The granules are coated with (b) (4) to mask the taste. The other excipients used in the drug product are microcrystalline cellulose and magnesium stearate. The capsule shell contains hypromellose. All excipients are USP- the National Formulary (NF) compendial excipients and the levels are within the inactive ingredient database limits for oral formulations. The CMC reviewers also concluded that impurities met ICH Q3B and hydrocortisone USP monograph requirements. CMC reviewers also found the Applicant's dissolution data for granules to be acceptable. Lastly, based on the dissolution data, CMC reviewers noted that the granules maintain their taste masking integrity with (b) (4) % of the drug intact after 5 minutes at pH (b) (4). The dissolution of the granules takes place over 45 minutes to get a cumulative dissolution of (b) (4) % of labeled drug at pH 1.2. Thus, the reviewers recommend to specify in the label that "the granules have to be given within 5 minutes [after mixing with food] to avoid bitter taste as the outer taste masking cover may dissolve".

An expiry of 36 months was granted when stored at room temperature (20⁰ C -25⁰C).

4. Nonclinical Pharmacology/Toxicology

Drs. Fred Alavi and Todd Bourcier, pharmacology/toxicology reviewers, recommend approval of the drug for the proposed indication (refer to the review in DARRTS from 8/28/2020).

No new non-clinical information was submitted; all non-clinical data is cross-referenced from FDA's findings of safety and effectiveness for Cortef (NDA 008697).

The quality attributes of the hydrocortisone granules drug substance did not identify any new safety concerns. The reviewers indicated that there were no unique or novel excipients in hydrocortisone granules formulation. All impurities were within specification limits and no new degradation products have been observed when drug product was stored.

5. Clinical Pharmacology

The clinical pharmacology review was completed by Drs. Mohammad Absar and Jayabharathi Vaidyanathan. The clinical pharmacology review team concluded that the study 007 established PK bioequivalence between hydrocortisone granules and Cortef and recommended approval of this NDA (refer to the review in DARRTS from 5/22/2020).

The clinical pharmacology characteristics of hydrocortisone granules were investigated in four studies conducted in dexamethasone-suppressed healthy adult volunteers and in one study conducted in pediatric subjects < 6 years old with AI:

- Study 007 (pivotal study) comparing bioavailability of hydrocortisone granules vs. Cortef in healthy adult volunteers in fed and fasted states.
- Study 001 evaluating PK of hydrocortisone granules following single dose of 10 mg administration and dose proportionality at doses 0.5 mg, 2 mg and 10 mg in healthy volunteers
- Study 002 evaluating absolute and relative bioavailability of hydrocortisone granules in healthy adult volunteers
- Study 006 evaluating the systemic exposure following single dose administration of hydrocortisone granules directly into the mouth vs. mixing with yogurt or soft food in healthy adult volunteers.
- Study 003 evaluating PK of hydrocortisone granules in pediatric subjects 0-6 years old with AI.

In addition, study 004 (extension study of study 003) was conducted in pediatric subjects < 6 years old with AI to evaluate long-term safety of hydrocortisone granules (discussed in Safety section below)

The to-be-marketed drug product formulation was used in the Applicant's studies.

The only study that compared PK characteristics between hydrocortisone granules and Cortef (reference drug) in order to establish PK bioequivalence and provide scientific bridge to Cortef was Study 007. This study and its results will be summarized next. All other studies will be referenced as needed.

PK bioequivalence between hydrocortisone granules and Cortef: Study 007

This was a two-part, single center, open-label, randomized, single-dose, two period, crossover relative bioavailability study of hydrocortisone granules versus Cortef in dexamethasone-suppressed healthy adult volunteers in the fasted (Part 1) and fed states (Part 2).

Each part included 2 treatment periods (1 and 2, where a single doses of hydrocortisone granules and Cortef were administered in a randomized sequence). There was at least a 7-day washout period (up to a maximum of 14 days) between dose administrations.

The primary objective of the study was to determine the relative bioavailability of hydrocortisone granules compared with Cortef based on serum cortisol concentrations in both fasted and fed states.

Fifty-one dexamethasone-suppressed subjects (26 fasted in Part 1 and 25 fed -in Part 2) received a single dose of each study drug: hydrocortisone granules 20 mg (content of four 5 mg capsules) and Cortef 20 mg. PK samples were collected up to 12 hours post-dose.

The Clinical Pharmacology reviewers reviewed the results of this study and concluded that study 007 demonstrated PK bioequivalence between hydrocortisone granules and Cortef and established a scientific bridge between hydrocortisone granules and Cortef: the 90% confidence interval of geometric mean ratio (GMR) for C_{max}, AUC_t and AUC_{inf} of serum cortisol were within the pre-specified acceptance criteria of 80 to 125% under both fasting and fed condition (Figure 1 and

Table 1).

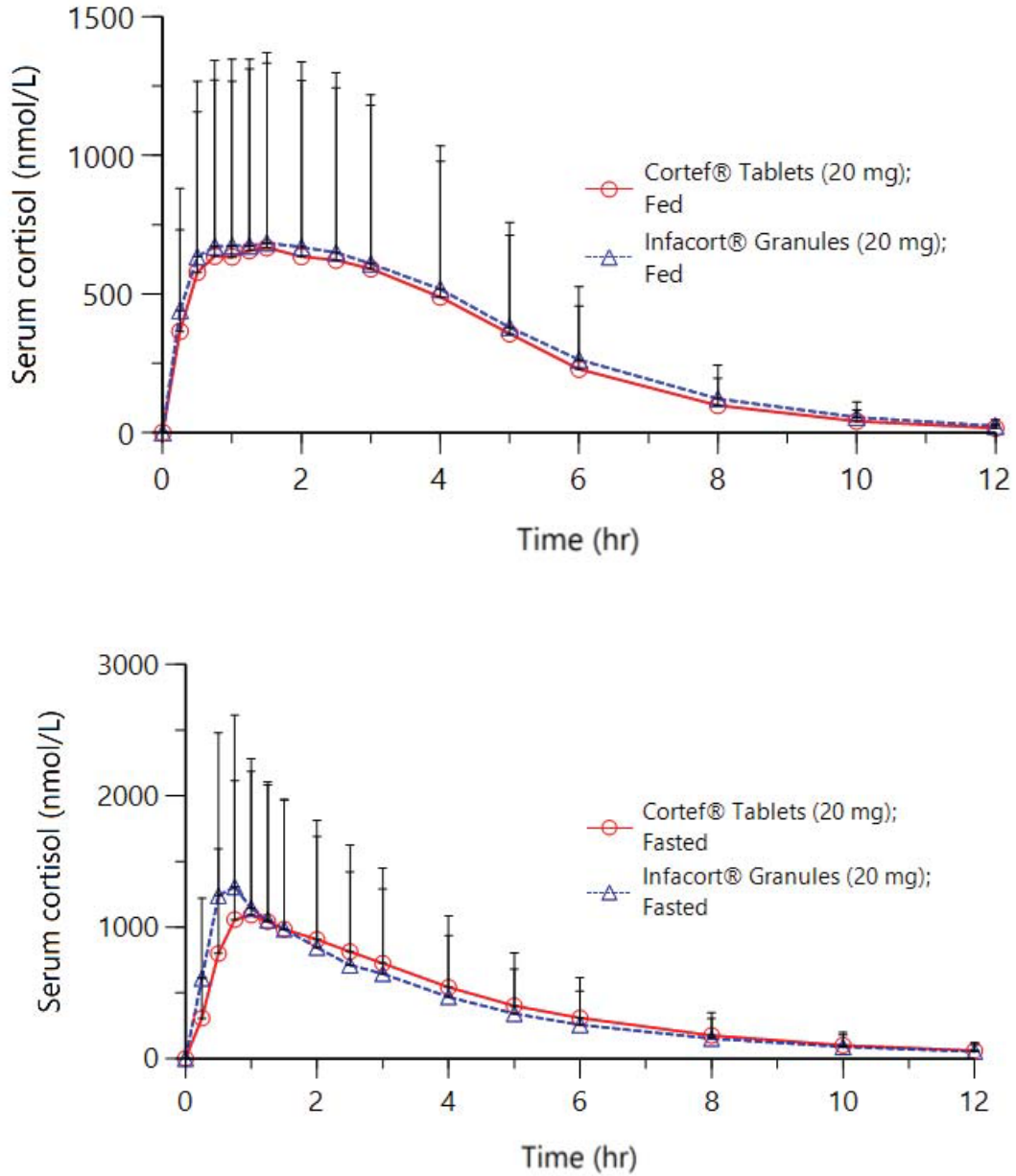
Appears this way on original

PK parameters	Hydrocortisone granules, mean (SD)	Cortef, mean (SD)	GMR (90% CI; hydrocortisone granules vs. Cortef)
PK parameters	Hydrocortisone granules, mean (SD)	Cortef, mean (SD)	GMR (90% CI; hydrocortisone granules vs. Cortef)
	Fasting condition	Fasting condition	
C _{max} (nmol/L)	1390 (513)	1270 (465)	109.54 (102, 117)
AUC _t (nmol.hr/L)	4750 (3160)	4900 (3020)	94.68 (88, 101)
AUC _{inf} (nmol.hr/L)	5020 (3630)	5190 (3460)	104.26 (97, 107)
	Fed condition	Fed condition	
AUC _t (nmol.hr/L)	4750 (3160)	4900 (3020)	94.68 (88, 101)
AUC _{inf} (nmol.hr/L)	5020 (3630)	5190 (3460)	104.26 (97, 107)
C _{max} (nmol/L)	744 (184)	838 (271)	90.53 (83, 98)
AUC _t (nmol.hr/L)	3770 (1510)	3510 (1150)	105.83 (100, 111)
AUC _{inf} (nmol.hr/L)	3850 (1620)	3630 (1190)	104.50 (99, 109)
AUC _t (nmol.hr/L)	3770 (1510)	3510 (1150)	105.83 (100, 111)
AUC _{inf} (nmol.hr/L)	3850 (1620)	3630 (1190)	104.50 (99, 109)

Table 1. Summary of statistical analysis of relative bioavailability (baseline-adjusted data, Study 007)

Source: Clinical Pharmacology review, table 2.

Figure 1. Plasma concentration-time curve of baseline-adjusted serum cortisol following single administration of 20 mg hydrocortisone granules and Cortef® under fasting (above) and fed (below) condition (Study 007).



Source: Clinical Pharmacology review, figure 1, page 9.

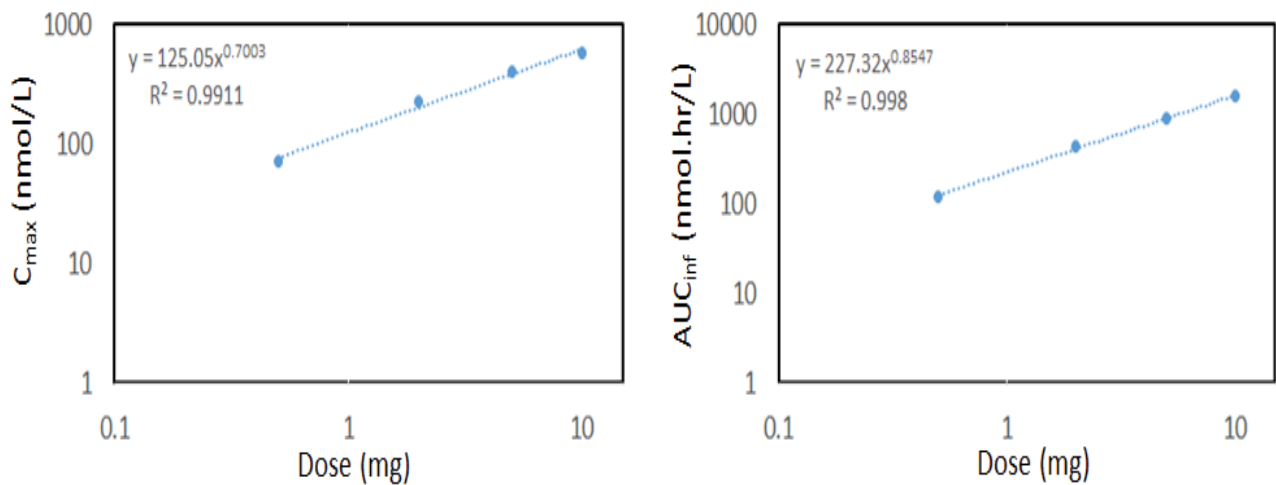
Pharmacokinetics of hydrocortisone granules

Based on Dr. Absar’s review of PK information from the submitted studies in healthy adult volunteers, hydrocortisone granules has the following PK properties.

T_{max} was 0.75 hour post-dose following the administration of single dose of 20 mg hydrocortisone granules. Baseline-adjusted AUC_t , AUC_{inf} and C_{max} were 4750 nmol.hr/L, 5020 nmol.hr/L and 1390 nmol/L, respectively. Absolute bioavailability of hydrocortisone granules was 87%. The $T_{1/2}$ of hydrocortisone granules is 2.05 ± 0.86 hours. The apparent volume of distribution was 38.6L. The plasma protein binding was not evaluated in the Applicant’s studies. However, Dr. Absar indicated that, based on published literature, 90-95% of plasma cortisol is bound to cortisol-binding globulin (CBG). Metabolism was also not investigated under the Applicant’s program. Hydrocortisone is metabolized in the liver and most body tissues to hydrogenated and degraded forms which are excreted in the urine, mainly conjugated as glucuronides.

Dose proportionality of hydrocortisone granules was evaluated at dose ranges 0.5-10 mg (Study 001). Serum cortisol concentrations increased in less than dose proportional manner (Figure 2).

Figure 2. C_{max} and AUC linearity with dose (Study 001)



Source: Clinical Pharmacology review, figure 6.

PK parameters of hydrocortisone granules in pediatric subjects with AI

The Applicant evaluated the absorption of hydrocortisone from hydrocortisone granules following the single oral administration of hydrocortisone granules in pediatric subjects < 6 years old with AI in Study 003 to characterize further PK profile of the hydrocortisone granules in the intended population.

Twenty-four subjects (6 subjects < 28 days old, 6 subjects- 28 days - < 2 years old and 12 subjects 2-6 years old) with confirmed AI by low cortisol levels and/or other tests were enrolled in the study. Majority of subjects had AI due to CAH (96% of subjects; 23/24 subjects), and one subject had AI secondary to hypopituitarism.

All subjects received the dose of hydrocortisone granules that was equivalent to the previous day's morning dose of hydrocortisone formulations used in these children. The range of previous hydrocortisone doses were 5.26-31.58 mg/m²/day; the majority of subjects (18/24 subjects) were on doses < 15 mg/m²/day. Dr. Lubas verified that previous doses and doses of hydrocortisone granules received in study 003 were similar. The higher than proposed doses for the replacement therapy in several subjects are explained by the fact that majority of subjects were receiving supraphysiologic doses of hydrocortisone to suppress adrenal sex steroid production and prevent the virilization symptoms associated with CAH. The capsules were opened, and the entire content was sprinkled on the back of the tongue and then was washed down with water, milk or juice. All subjects were fasting for at least 2 hours prior to the dose administration.

Blood cortisol was collected at 30, 45, 90, 120, 150, 180, and 300-minute time points post dose. The primary endpoint was the maximum cortisol concentration up to 240 minutes post-dose (from one of two samples collected at 60 and 240 minutes).

The results of the study demonstrated that hydrocortisone was well absorbed from hydrocortisone granules. All subjects had baseline serum cortisol < 150 nmol/l (5.4 mcg/dl) that confirms the diagnosis of AI. The increase from baseline in C_{max} was observed at 60 minutes post-dose in all subjects and 60-minute cortisol levels after dosing were > 150 nmol/l (27 mcg/dl) in all subjects (Table 2. Proportion of subjects with cortisol levels higher than at baseline (Study 003)). These levels are within normal morning cortisol levels in subjects without adrenal insufficiency (> 18 mcg/dl).¹⁵

The reviewers also indicated that the median level of cortisol observed at 60-minute time point (535 nmol/l (19.4 mcg/dl)) in pediatric subjects was consistent with the levels following hydrocortisone administration reported in published literature for adult and pediatric patients with AI (691 nmol/l (25 mcg/dl) and 551 nmol/l (20 mcg/dl), respectively).¹⁶ No adverse events of adrenal insufficiency were reported in any of subjects.

Table 2. Proportion of subjects with cortisol levels higher than at baseline (Study 003)

¹⁵ Stefan R. Bornstein, Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 2016; 101 (2): 364–389

¹⁶ Peters CJ et al. Deconvolution analysis of 24-h serum cortisol profiles informs the amount and distribution of hydrocortisone replacement therapy. *Clin Endocrinol*. 2013;78(3):347-51

Time	Cohort 1 ¹	Cohort 2 ¹	Cohort 3 ¹	Overall
	N=12	N=6	N=6	N=24
	Number of subjects (% of subjects in Cohort with non-missing values)			
C_{max}	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
	p=0.0005	p=0.0313	p=0.0313	p<0.0001
60 minutes	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
	p=0.0005	p=0.0313	p=0.0313	p<0.0001
240 minutes	12 (100.0)	2 (40.0) ²	5 (83.3)	19 (82.6) ³
	p=0.0005	p=1.0000	p=0.2188	p=0.0026

¹ Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days

² n=5; Subject (b) (6) Cohort 2) had no result at 240 minutes.

³ n=23; Subject (b) (6) Cohort 2) had no result at 240 minutes.

Note: Below the limit of quantification was set to the lower limit of quantification (i.e. 14.10 nmol/L, 5.11 ng/mL) for baseline samples and zero for post-baseline samples.

Source: Clin.Pharm review, table 3.

In conclusion, although this study was not a pivotal study for the proposed indication, these data provide reassurance that cortisol levels following hydrocortisone granules administration in pediatric subjects increase sufficiently to minimize the risk of adrenal insufficiency.

The Applicant used the adult PK data to model dosing and compare drug elimination characteristics in children of all ages (0-18 years). The reviewers reviewed the results of this analysis and concluded that based on the absorption, distribution, metabolism, and excretion (ADME) characteristics of hydrocortisone, the PK in older children, 6-17 years old, is not expected to be different as compared to adults or to children < 6 years old. The reviewers also concluded that the results of population-based PK (PBPK) model analysis demonstrated that the dose of 10 mg/m²/day in children results in similar exposure compared to adult patients receiving 20 mg dose (the recommended adult dose for the treatment of AI¹⁷). The results of the analysis also demonstrated that children < 2 years old have 2.3-fold higher clearance of hydrocortisone compared to older children, thus, younger children may require more frequent dosing.

Food effect

The food effect on systemic exposure to hydrocortisone granules was evaluated in Study 006. The reviewers concluded that the study demonstrated that 90% confidence interval of GMR for C_{max}, AUC_t and AUC_{inf} of serum cortisol were within the pre-specified acceptance criteria of 80 to 125% when the drug was administered with yogurt or apple sauce as compared to administering directly into the mouth (Table 3).

Table 3. Summary of statistical analysis of relative bioavailability of hydrocortisone granules administered directly into the mouth, with soft food or yogurt (baseline-adjusted; Study 006).

¹⁷ Stefan R. Bornstein, Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2016; 101 (2): 364–389

PK Parameter	Test/Reference Ratio and 90% CI	
	Soft Food/back of the tongue (n=18)	Yoghurt/back of the tongue (n=18)
C _{max} (nmol/L)	99.68 (93.98 – 105.72)	99.43 (94.33 – 104.80)
AUC _{0-t} (h*nmol/L)	98.24 (94.42 – 102.21)	103.33 (94.80 – 112.62)
AUC _{0-inf} (h*nmol/L)	98.21 (94.24 – 102.36)	103.07 (94.55 – 112.35)
Median Difference and 95% CI		
T _{max} (h)	0.13 (0.00 – 0.25)	0.13 (0.00 – 0.25)

C_{max} and AUC data presented is Geometric LSMeans Test/Reference Ratio (90% CI) for both Test IMP administrations. Results obtained using ANOVA with fixed effects for sequence, period, treatment and subject (sequence) (excl. T_{max}). T_{max} data presented is Median Difference (95% CI) for both Test IMP administrations.

T_{max} results obtained using the Wilcoxon Signed-Rank test and Hodges-Lehman test.

Source: Table 4, Clinical Pharmacology review.

Thus, the administration with food is acceptable and granules can be mixed with food to facilitate the drug administration in younger children who have difficulties with swallowing granules.

Intrinsic Factors that could Influence Exposure

The clinical pharmacology reviewers indicated that no dose adjustment is required based on gender, age, race, hepatic or renal impairment.

Drug-Drug Interaction (DDI)

No dedicated DDI studies were conducted by the Applicant. The Applicant proposed to include information regarding DDI from Cortef label. The reviewers found this approach overall acceptable, but had additional recommendations:

- The reviewers noted that Cortef label contains a potential interaction of hydrocortisone with aspirin that has not be included in hydrocortisone granules label and recommend to include the following language:
“Corticosteroids may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids.”
- Since hydrocortisone is metabolized by hepatic enzymes, the reviewers also recommend monitoring patients who are concurrently taking drugs that induce or inhibit CYP3A4 enzymes and adjust hydrocortisone granules doses accordingly.

The potential risk of underdosing associated with the swallowing of the capsule as whole

As requested during Type C meeting on 2/6/2019 (refer to regulatory section above), the Applicant included in NDA the in vitro dissolution profile to address the risk of underdosing associated with swallowing the capsule as a whole and to demonstrate that that the capsule product behaves as an immediate-release product when swallowed as whole. The reviewers found the submitted data to be sufficient to conclude that systemic exposure from the

administration of intact capsule will be similar to the systemic exposure from the administration of granules. The reviewers did not recommend conducting the in-vivo study at this time comparing PK parameters between intact capsule and granules.

Dosing regimen

The reviewers concluded that the starting doses of hydrocortisone granules 8-10 mg/m²/day for patients with AI are acceptable. The daily basal cortisol production rate in healthy children has been shown to range 6.1 ±1.8/m² - 7.31 ±1.8 mg/m²/day.¹⁸ The doses should be individualized based on clinical signs and symptoms (cortisol levels should not be used for the titration). The lowest effective dose should be used to minimize the risks of adverse events associated with the use of supraphysiologic doses. In general, doses of hydrocortisone of > 15 mg/m²/day were associated with growth suppression in children with CAH.^{19 20} The reviewers also concluded that the proposed replacement doses are in line with the most recent recommendations by scientific societies.²¹ Based on the results of the PK and food interaction studies, the reviewers also recommend administering granules directly onto the child's tongue or into a spoon and place in child's mouth.

I agree with the reviewers' recommendations regarding the proposed doses and that the doses should be individualized given the fact that drug is titrated to the effect and the desired effect may be reached with the lowest dose in these patients and the clinical symptoms are monitored during therapy. However, I recommend administering hydrocortisone granules in 2-3 divided doses (not in four divided doses). The Applicant's proposed regimen of 4- times a day dosing does not mimic normal circadian rhythm of cortisol and additional dose administered at midnight carries higher risk of over-replacement. The normal circadian rhythm of cortisol is associated with peak levels in the morning and undetectable levels at night²². Thus, three time a day dosing is the most physiologic and also the most commonly used regimen in general practice for the treatment of AI.²³ In addition, the administration of the late-night dose is associated with inconvenience to patients and potential risk of choking, since patient has to be

¹⁸ Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. *J Pediatr.* 1990 Dec;117(6):892-6.

¹⁹ Silva IN, Kater CE, Cunha CF, Viana MB. Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia. *Arch Dis Child.* 1997 Sep;77(3):214-8

²⁰ Bonfig W, Pozza SB, Schmidt H, Pagel P, Knorr D, Schwarz HP. Hydrocortisone dosing during puberty in patients with classical congenital adrenal hyperplasia: an evidence-based recommendation. *J Clin Endocrinol Metab.* 2009 Oct;94(10):3882-8.

²¹ Stefan R, Bornstein, Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016; 101 (2): 364–389

²² Weitzman E.D., Fukushima D., Nogeire C., Roffwarg H., Gallagher T.F., Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab.* 1971

²³ Whitaker MJ, Spielmann S, Digweed D, et al. Development and testing in healthy adults of oral hydrocortisone granules with taste masking for the treatment of neonates and infants with adrenal insufficiency. *J Clin Endocrinol Metab.* 2015;100:1681-1688

fully awake to swallow the granules. The three-times a day regimen is further supported by the data from study 004 where all pediatric subjects tolerated well hydrocortisone granules administered three times daily without signs and symptoms of AI. The fact that five subjects discontinued the study preliminary because their caregivers did not like to wake up children at night to administer the last dose (according to the strict 8-hour schedule) further demonstrates the inconvenience with four-times-a day regimen where the last dose has to be administered at midnight.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There are no new clinical efficacy data essential for the risk/benefit assessment of hydrocortisone granules. Dr. William Lubas, clinical reviewer, concluded that the Applicant sufficiently justified the appropriateness of the reliance on FDA's finding of safety and effectiveness for Cortef (based on the results of BE study 007) to support approval of Hydrocortisone granules for the AI indication in pediatric patients. He recommended approval of this NDA (refer to clinical review in DARRTS from 9/2/2020).

The Sponsor submitted additional data from two pediatric studies in children < 6 years old with AI to support the use of hydrocortisone in the intended population: single dose, PK study (Study 003; discussed in Clinical Pharmacology section above) and long-term, safety, single arm study (Study 004; discussed in Safety section below). In these studies, hydrocortisone granules were administered to all subjects by sprinkle granules over the food or by administering them directly into the mouth and in doses equivalent to their previous doses of hydrocortisone formulations. Although both studies were not designed to evaluate the efficacy of hydrocortisone granules in intended population and there were no control group, the findings from both studies provide reassuring evidence that hydrocortisone granules, when administered as directed, increases sufficiently blood cortisol levels (study 003) and prevent signs and symptoms of adrenal insufficiency. No adverse events of adrenal insufficiency were reported in these children who were treated with hydrocortisone granules for up to 2.5 years.

8. Safety

Corticosteroid formulations have a long history of use as a replacement therapy in adrenal insufficiency and as anti-inflammatory and immunosuppressive agents for the treatment of various allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, etc. conditions.

The major safety concerns with all corticosteroid formulations, including hydrocortisone formulations are the adverse effects that are associated with under or over treatment. The

severity of these adverse effects depends on the dose and duration of treatment. Side effects of long-term (>3 months) supra-physiological corticosteroid therapy include weight gain, hyperglycemia, increased blood pressure, reduced bone mineral density and bone fractures, acne, hirsutism, gastrointestinal symptoms, cataracts, immunosuppression, behavioral changes, Cushingoid appearance. In children, chronic corticosteroid therapy with excessive doses (> 15-20 mg/m²/day^{24 25}) also results in decreased linear growth and short stature, as well as delayed puberty. Signs and symptoms of inadequate corticosteroid replacement include fatigue, joint and muscle pain, weight loss, poor appetite, low blood pressure, hypoglycemia and other signs and symptoms of adrenal insufficiency. Stressors known to increase cortisol requirement (eg. trauma, surgery, acute illness) may also trigger adrenal insufficiency in patients with AI on stable GC doses. Lastly, the addition of medications that alters cortisol clearance (e.g., thyroid hormones, growth hormones) may also trigger adrenal insufficiency. Thus, increasing corticosteroid doses is recommended during periods of stress and with co-administration of the concomitant medications that affect cortisol clearance.²⁶

The safety of hydrocortisone granules is primarily supported by the established safety profile for Cortef tablets. The Applicant has provided additional safety information from the PK studies in healthy adults and from study 004, an open label, long term study evaluating safety of hydrocortisone granules in pediatric subjects with AI < 6 years old who completed study 003. However, it should be noted that the results from these studies do not add substantive safety information due to the multiple study limitations including dosing over a short period of time (mostly single dosing), different population (mostly healthy adults), absence of controlled group (study 004), etc. Thus, this memorandum will only briefly discuss safety observations made in these studies.

Overall, 124 subjects received at least one dose of hydrocortisone granules in Applicant's studies conducted to date. Of these, 100 subjects were healthy adults who received a single dose of hydrocortisone granules (range 0.5mg-10 mg). Twenty-four of 124 subjects were children < 6 years old with AI who received single dose (24 subjects; Study 003) or multiple doses of hydrocortisone granules (18/24 subjects; Study 004) for up to 26 months. Refer to the Clinical Pharmacology section above for discussion on the study 003 design and PK results.

Study 004

Study 004 was a single arm, open label, long-term safety study of hydrocortisone granules in pediatric subjects < 6 years old with AI. The primary objective of the study was to collect a

²⁴ Silva IN, Kater CE, Cunha CF, Viana MB. Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia. Arch Dis Child. 1997 Sep;77(3):214-8

²⁵ Bonfig W, Pozza SB, Schmidt H, Pagel P, Knorr D, Schwarz HP. Hydrocortisone dosing during puberty in patients with classical congenital adrenal hyperplasia: an evidence-based recommendation. J Clin Endocrinol Metab. 2009 Oct;94(10):3882-8. doi: 10.1210/jc.2009-0942

²⁶ Guidelines

prospective safety data in these subjects by reporting the adverse events. Subjects previously enrolled in study 003 were eligible to continue treatment with hydrocortisone granules in study 004. Of 24 subjects who completed study 003, six subjects were not enrolled in study 004 because of the inconvenience with frequent visits (5 subjects) and one subject terminated the study participation because of AE of vomiting in study 003. Additional 6 subjects discontinued study 004 preliminary: 5 subjects (on Days 1-150) - due to the inconvenient dosing at night and one subject on the first day because the subject spat out the first dose. Of 18 subjects enrolled in study 004, 9 subjects were < 6 years but > 2 years old, 6 subjects were < 2 years old but > 28 days old and 3 subjects were < 28 days old. All subjects received hydrocortisone granules in doses that were equivalent to the previous doses of hydrocortisone used for the treatment of AI in these subjects; the daily doses were administered in three divided doses. Mean daily dose of hydrocortisone granules in Study 004 was ~ 11 mg/m² at the end of treatment (~2.5 years). The subjects had clinic visits monthly during the first 2 months, and every 3 months thereafter.

Death

No deaths were reported in all Applicant's studies

SAEs

Nine SAEs were reported in 3 pediatric subjects in study 004. One subject had 5 SAEs (3 events of gastroenteritis and 2 events of vomiting), one subject had SAE of urinary tract infection and one subject has SAE of erysipelas due to jellyfish sting. All events were considered as related to the study drug.

However, the SAEs of gastroenteritis and vomiting in 5-year old subject is concerning and may represent the event of adrenal insufficiency, but without cortisol levels at time of the events no firm conclusion can be made. These symptoms are also not specific and may be due to the presence of underlying medical condition (constipation) or gastroenteritis due to infection/food intolerance that is common in this age group. Lastly, all events resolved, and subject continued to participate in the study. Overall, adrenal insufficiency is a well-recognized adverse reaction with use of all corticosteroids (especially during the stress events) and is monitorable event, and can be mitigated by appropriate labeling, monitoring and treatment with dose increase and/or treatment with injectable corticosteroids. The risk of adrenal insufficiency is included in the WARNING and PRECAUTIONS section of the label.

I agree that all other SAEs were not drug-related.

No SAEs were reported in other Applicant's studies.

AEs leading to study discontinuations

No AEs that led to the drug discontinuation were reported in any of the studies.

Common adverse reactions

Overall, the drug was well tolerated by all subjects and no new drug-specific safety concerns were reported in all Applicant's studies.

The AEs that occurred in more than 1 subject in a single dose pediatric study 003 were diarrhea (12.5%, 3 subjects), vomiting and rash due to mosquito bite (2 subjects, 8%, each). All events of vomiting occurred 1.5- 6 hours after dosing and were considered as unrelated to the drug. All other AEs occurred in 1 subject each (infantile spitting up, fatigue, hyperhidrosis).

The most frequent AEs in long-term safety study 004 were pyrexia (10 subjects with 45 events), gastroenteritis (9 subjects with 15 events), viral upper respiratory tract infection (7 subjects with 21 events) and vomiting (7 subjects with 14 events) (Table 4).

Table 4. AEs occurring in ≥ 2 of subjects treated with hydrocortisone granules in Study 004

Preferred Term	N of subjects	%
Pyrexia	10	56
Gastroenteritis	9	50
Viral upper respiratory tract infection	8	44
Vomiting	7	39
Viral infection	6	33
Conjunctivitis	5	28
Otitis media viral	3	17
Tonsillitis	3	17
Body temperature increased	2	11
Bronchitis	2	11
Dental caries	2	11
Diarrhea	2	11
Genitourinary operation	2	11
Pharyngitis	2	11
Respiratory tract infection	2	11
Rhinitis	2	11

Source, Clinical Review, Table 18.

No events of AI were reported during the study. No Cushingoid features (e.g., increase in weight, hyperglycemia) were reported during the 2.5-year treatment period.

Clearly, these types of AEs (e.g., infections, fever, gastroenteritis) are frequently observed and overall expected in this age group; however, a lack of comparator for this analysis limits overall conclusions regarding causality of these AEs. For example, such AEs as gastroenteritis and vomiting are frequently observed in young children and usually have viral etiology, however, these symptoms are non-specific and may be due to underdosing. No firm conclusion can be made in the absence of serum cortisol levels at time of the event(s) and other symptoms of AI (e.g., hypotension, hypoglycemia, electrolyte abnormalities). Thus, I recommend including in the label all AEs that occurred in the study that were reported in more than 2 subjects.

One of the major safety concerns in children with use of all corticosteroids in supraphysiologic doses for a long time is suppression of growth. Thus, the Applicant collected prospective growth data in all subjects participated in study 004. No growth suppression was observed in 16/18 subjects as evaluated by Z-scores at the end of the study; the Z scores remained within -2SDS-+2SDS range (predefined Applicant's criteria). Two subjects had Z-scores of < -2 SDS, but the causality assessment is confounded in both subjects by the underlying medical conditions that may be associated with growth delay: renal hypoplasia and hypopituitarism with growth hormone deficiency.

The Applicant also evaluated the use of hydrocortisone granules during the stress events of illness or surgery when increase in dose is required (i.e. "sick day rule implementation"). Thirteen subjects (72%) had required temporary increase in hydrocortisone dose on sick days during the study. The events that led to increase hydrocortisone dose were fever (13 subjects), vomiting (5 subjects), diarrhea (2 subjects) and "other" (10 subjects). Dr. Lubas further evaluated the "other" AEs that led to "sick day rule implementation"; these AEs were infections, surgery, dental procedures, injuries and emotional and physical stress (e.g., starting kindergarten, prolong activity after hiking, birthday party, etc.). All events resolved with appropriate treatment and no adrenal crisis were reported during the events.

Lastly, Division of General Endocrinology (DGE) had consulted Division of Pharmacovigilance (DPV) to provide analysis of the adverse events associated with hydrocortisone use in children < 18 years old with AI or CAH identified in FDA Adverse Event Reporting System (FAERS) to obtain additional safety data on use of hydrocortisone in children with AI (refer to DPV review in DARRTS from 6/29/2020). DPV reviewers concluded that the majority of AEs reported in FAERS were consistent with already labeled events in Cortef label (e.g., adrenal insufficiency, cushingoid appearance, vomiting, fatigue, cataract, growth retardation). The reviewers identified four AEs of interest: gastric pneumatosis, left ventricular (LV) hypertrophy, malabsorption due to polyethylene glycol (PEG) and drug-drug interaction with ethosuximide. After the discussion with clinical and clinical pharmacology reviewers, all of these AEs were considered as not related to hydrocortisone use. LV hypertrophy and gastric pneumatosis were most likely due to the underlying medical conditions including prematurity. Clinical pharmacology reviewer indicated that due to the fact that hydrocortisone is rapidly absorbed from GI tract, it is unlikely that PEG administered 2 hours after hydrocortisone administration affected hydrocortisone absorption. Lastly, Clinical Pharmacology also did not find compelling evidence from single case report that co-administration of ethosuximide (for seizures) with hydrocortisone increased clearance of hydrocortisone.

Risk of choking associated with swallowing capsule as whole

One of the potential formulation-specific safety concerns with use of hydrocortisone granules packed in capsules is risk of choking and/or underdosing if capsule is swallowed as whole.

Clinical Pharmacology reviewers confirmed that there is no risk of underdosing if capsule is swallowed as whole (refer to Clinical Pharmacology section above).

No adverse reactions of choking associated with use of hydrocortisone granules were reported to date in all Applicant's studies. In addition, as requested during the Type C meeting on 2/6/2019 (refer to Regulatory History section above), the Applicant included an analysis of adverse events associated with hydrocortisone granules approved for use in children with AI in EU obtained from three post-marketing periodic benefit-risk evaluation reports covering period from 2/2018 through 8/2019. There were no events of choking reported to date, however, the data should be interpreted with caution since, there was no prespecified plan of data collection and evaluation provided by the Applicant. There were several reports of medication errors including swallowing of the capsule as whole (2 children of school age), spread of the granules over the lips instead of mouth (2-week old), inability of getting all the granules out after the wetting the rim of capsule with saliva ((8 -year old), combining the content of two capsules in one capsule (12-year old). No AI was reported in any cases of medication errors. The swallowing of the capsule as whole is the most concerning medication error since it represents the misuse of the drug that may lead to the choking. Dr. Lubas reviewed all data and did not reveal any new safety concerns with hydrocortisone itself.

The potential risk of choking is also discussed in detail in the CMC, clinical, DPMH and DMEPA reviews (refer to corresponding reviews in DARRTS). All reviewers agreed that this potential risk can be mitigated through the proper labeling of the product that include clear administration instructions and warnings that the capsule should not be swallowed as whole and through enhanced pharmacovigilance (EPV).

In conclusion, the safety profile of hydrocortisone granules is expected to be consistent with the established safety profile for Cortef described in the current product label and with corticosteroid class effects. No new safety signals were found in the clinical studies conducted by the Applicant with hydrocortisone granules. The potential formulation-specific safety concern is the risk of choking if the capsule is swallowed as whole. No adverse reactions were reported with swallowing of the capsule as whole in the Applicant's clinical program to date. Overall, the benefit of the proposed hydrocortisone formulation to allow for more accurate dosing in children outweighs the theoretical risk of choking if capsule is swallowed. The potential risk of choking can be adequately mitigated through the appropriate labeling including detailed instructions on administration of the drug. In addition, the post-marketing reports should be monitored for medication errors related to swallowing of the capsule as whole through enhanced pharmacovigilance and this issue should be revisited if the need arises.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

10. Pediatrics

The intended indication is for the treatment of pediatric patients with AI. In addition, hydrocortisone granules has received orphan-drug designation in May 2015. Therefore, the requirements of the Pediatric research Equity Act do not apply to this application.

11. Other Relevant Regulatory Issues

Office of Study Integrity and Surveillance (OSIS) inspection

OSIS conducted a remote record review (RRR) of the clinical portion of pivotal study 007 and analytical portion of Study RD 318/33181H conducted at [REDACTED] (b) (4)

[REDACTED] An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic. OSI did not observe any objectionable findings during the RRR and concluded the data from the audited studies are reliable (refer to review in DARRTS from 8/27/2020).

Financial Disclosure

Financial disclosure documentation was reviewed by Dr. Lubas. He did not identify any issues that could influence the outcome of the trials.

Proprietary name

The proposed proprietary name, Alkindi, was found to be acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on 2/14/2020.

Division of Pediatric and Maternal Health (DPMH) Consult

Division of General Endocrinology (DGE) had consulted DPMH to provide an input on the proper format and content of the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections of hydrocortisone granules labeling to follow the Pregnancy and Lactation Labeling Rule (PLLR).

DPMH revised relevant sections of labeling for compliance with the PLLR and for compliance with the PLLR and provided labeling recommendations (refer to DPMH review from 8/25/2020 in DARRTS). I agree with all DPMH recommendations.


Lastly, DPMH also concluded that the use of physiologic doses of hydrocortisone is not expected to cause major birth defects, miscarriage, and adverse maternal and fetal outcomes. Therefore, DPMH does not recommend a postmarketing pregnancy safety study at the current time.

12. Labeling

Prescribing Information

At the time of this review, labeling negotiations were ongoing.

- **INDICATIONS AND USAGE:**
 - The indication should be for the replacement therapy in pediatric patients with adrenocortical (adrenal) insufficiency. The reference to the type of adrenal insufficiency, i.e. primary, secondary, due CAH, should be removed from the indication. Adrenal insufficiency is due to decreased corticosteroid production by adrenal gland regardless of the cause (due to hemorrhage, trauma, surgery, infection, CAH, etc.) or type (primary, secondary, tertiary) and efficacy and safety of the replacement therapy with hydrocortisone granules is expected to be the same in all types of AI.
- **DOSAGE AND ADMINISTRATION:**
 - The recommended starting dose is 8-10 mg/m². The dose titration should be individualized. Younger patients may require higher starting doses due to increase clearance of hydrocortisone in this population. The lowest effective dose should be used to avoid AEs associated with over-replacement including the suppressed growth. The doses should be temporarily increased during the situations associated with increased stress such as acute illness, surgery, trauma.
 - I do not recommend separate starting doses of 10-15 mg/m² for the treatment of AI in subpopulation of patients with CAH. These doses are required to suppress the adrenal sex steroid production and to treat CAH symptoms associated with adrenal sex steroid overproduction (e.g., hirsutism, virilization, precocious puberty). Since the proposed indication for hydrocortisone granules is the treatment of adrenal insufficiency only, the lower replacement doses are sufficient to treat signs and symptoms of AI associated with CAH.
 - The total daily dose of hydrocortisone granules should be administered 2-3 times a day in divided doses with highest dose in the morning and lowest dose in late afternoon. Such regimen mimics normal circadian rhythm of cortisol. The Applicants' proposed 4-times a day dosing regimen requires the last dose administration to occur at midnight, thus it is not physiologic and may be associated with over-replacement.
 - The Dosage and Administration section provides adequate instructions to mitigate the risk of medication errors and possible adverse reactions associated with medication errors.
- **Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:**
 - **WARNING** and **PRECAUTIONS** section appropriately describes class specific adverse reactions associated with corticosteroid use including increased risk of adrenal insufficiency associated with undertreatment and risks of Cushing's syndrome, hyperglycemia, suppressed growth, infections associated with use of supraphysiologic doses for prolonged time.
- **CLINICAL STUDIES** section:

○  (b) (4)
I recommend including PK findings in children with AI from study 003 in section 12 of the label (Clinical Pharmacology section)

Other Labeling

Medication Guide was reviewed by DMEPA and OPDP reviewers who provided further recommendations including the detailed instructions on the administration of the drug.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

REMS are not needed for hydrocortisone granules for the proposed indication. All risks are appropriately labeled in the label to inform caregivers, patients and prescribers and to mitigate risks associated with use of this drug.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No safety findings prompt the need for Postmarketing Requirements and Commitments.

Based on team recommendations (refer to Safety section above), the plan for enhanced pharmacovigilance in postmarketing settings in order to assess the risk of choking, aspiration, and incorrect drug administration technique related to swallowing of the capsule as whole was discussed with the Applicant.

14. Recommended Comments to the Applicant

The request for EPV should be added to the Action Letter.

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/

MARINA ZEMSKOVA
09/25/2020 02:43:07 PM

THERESA E KEHOE
09/26/2020 11:26:12 AM
I concur with the regulatory decision outlined in this memo