CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213876Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 25, 2020
To:	Jennifer Johnson Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	AKLINDI SPRINKLE (hydrocortisone)
Dosage Form and Route:	granules, for oral use
Application Type/Number:	NDA 213876
Applicant:	Covance, US agent on behalf of Diurnal Limited

1 INTRODUCTION

On November 29, 2019, Diurnal Limited submitted for the Agency's review a New Drug Application (NDA) #213876 ALKINDI SPRINKLE (hydrocortisone) granules, for oral use. The proposed indication for ALKINDI SPRINKLE (hydrocortisone) granules is for the treatment of pediatric adrenal insufficiency.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of General Endocrinology (DGE) on July 8, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ALKINDI SPRINKLE (hydrocortisone) granules, for oral use.

2 MATERIAL REVIEWED

- Draft ALKINDI SPRINKLE (hydrocortisone) MG and IFU received on November 29, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 16, 2020.
- Draft ALKINDI SPRINKLE (hydrocortisone) Prescribing Information (PI) received on November 29, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 16, 2020.
- Approved CORTEF (hydrocortisone) comparator labeling dated November 21, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information

- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
09/25/2020 12:59:29 PM
DMPP-OPDP review of hydrocortisone granules (ALKINDI SPRINKLE) NDA 213876 MG and IFU

ANKUR S KALOLA
09/25/2020 02:38:32 PM

SHARON W WILLIAMS
09/25/2020 02:42:45 PM

LASHAWN M GRIFFITHS
09/25/2020 02:49:11 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 23, 2020

To: Jennifer Johnson, Regulatory Project Manager
Division of General Endocrinology (DGE)

Monika Houstoun, Associate Director for Labeling, (DGE)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for ALKINDI® SPRINKLE (hydrocortisone) oral granules

NDA: 213876

In response to DGE's consult request dated July 8, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for ALKINDI® SPRINKLE (hydrocortisone) oral granules.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DGE (Jennifer Johnson) on September 16, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DGE (Jennifer Johnson) on September 17, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

24 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

ANKUR S KALOLA
09/23/2020 09:50:59 AM

M E M O R A N D U M

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

DATE: August 27, 2020

TO: Ellis F. Unger, M.D.
Director
The Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs Clinical (OND Clinical)
Office of New Drugs (OND)

FROM: Hasan A. Irier, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Xikui Chen, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Acting Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote Record Review (RRR) of (b) (4)

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the clinical portion of study Infacort 007 (NDA 213876, Infacort® granules) and analytical portion of Study RD 318/33181H (NDA 213876, Infacort® granules) conducted at (b) (4) An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

We did not observe any objectionable findings during the RRR that impact reliability of study data.

1.1. Recommendation

Based on our review of the RRR findings, we conclude the data from the audited studies are reliable.

2. Reviewed Studies

Study Infacort 007 (NDA 213876)
"A two-part, single center, open-label, randomized, single-dose, two period, crossover, relative bioavailability study of Infacort® versus Cortef® in dexamethasone-suppressed healthy adult male and female subjects in the fasted and fed states"
Clinical Study Period: 4/16/2018 - 7/13/2018

Study RD 318/33181H (NDA 213876)
"Determination of Cortisol in human serum by liquid chromatography - tandem mass spectrometry (LC-MS-MS)"
Sample Analysis Period: 5/31/2018 – 7/25/2018

3. Scope of RRR

OSIS Pharmacologists Hasan A. Irier and Xikui Chen reviewed the clinical and analytical portions of the above studies conducted at (b) (4) and the analytical site formerly known as (b) (4) from (b) (4).

The clinical RRR included a thorough examination of study records, subject screening records, informed consent process, protocol deviations, independent ethics committee approvals, correspondence, test article accountability and storage, randomization, adverse events, case report forms, blood sample collection, serum sample preparation, and interviews with the firm's management and staff.

OSIS (DSI) previously conducted clinical inspection at this site in (b) (4) for NDA (b) (4). The inspection resulted in VAI classification, for not excluding some subjects that should have been excluded per protocol. Suitable corrective actions were implemented after the inspection.

The analytical RRR included an examination of study records, method validations, serum sample analyses, and interviews with the firm's management and staff.

OSIS did not previously conduct analytical inspections at this site.

4. RRR Findings

At the conclusion of the RRR, we did not observe any objectionable conditions that impact reliability of study data. No items were discussed with firm's management during the RRR close-out meeting.

5. Conclusion

After review of the RRR findings, we conclude that data from the audited studies are reliable.

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Choi/Skelly/Au/Irier/Chen

Draft: XC 8/24/2020; HAI 8/24/2020
Edit: MFS 8/24/2020; KAB 8/26/2020

ECMS:
Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL [redacted]

Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/ [redacted]

OSIS File #: [redacted] (NDA 213876)
FACTS: [redacted]

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/s/

XIKUI CHEN
08/27/2020 01:50:30 PM

HASAN A IRIER
08/27/2020 02:01:43 PM

MICHAEL F SKELLY
08/27/2020 02:03:17 PM

KIMBERLY A BENSON
08/27/2020 03:28:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: 08/24/2020 **Date consulted:** 07/14/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of General Endocrinology (DGE)

Drug: Alkindi Sprinkle (hydrocortisone) granules

NDA: 213876

Applicant: Diurnal Limited

Subject: Pregnancy and Lactation Labeling

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

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 213876
- Applicant's IR Response, submitted July 30, 2020
- Applicant's Proposed PLLR Labeling, submitted July 30, 2020
- DGE consult form for DPMH, DARRTS Reference ID 4640912

- DPMH review of Pandel (hydrocortisone probutate) cream 0.1%, NDA 20453, on December 8, 2016. DARRTS Reference ID 4025609.
- DPMH review of Orapred ODT (prednisolone sodium phosphate orally disintegrated tablets), NDA 21959. October 11, 2019. DARRTS Reference ID 4505465.

(b) (4)

Consult Question: The Division would like DPMH to review and provide comments regarding the proposed PLLR portion of the product insert.

INTRODUCTION AND BACKGROUND

On November 29, 2019, the applicant (Diurnal Limited) submitted a new NDA application for Alkindi Sprinkle (hydrocortisone) granules. The Division of General Endocrine (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) on July 14, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- On November 29, 2019, the applicant submitted a new NDA for Alkindi Sprinkle (hydrocortisone), NDA 213876, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Alkindi has a proposed indication of replacement therapy of adrenal insufficiency (AI) in infants, children and adolescents (from birth to <17 years old). The Referenced Listed Drug (RLD) is Cortef (hydrocortisone, NDA 8697) tablet, which was approved December 15, 1952.
- On May 13, 2015, Alkindi Sprinkle was granted Orphan designation.
- On July 20, 2020, an information request (IR) was sent to the applicant to obtain labeling in PLLR format, as well as a review of literature regarding the use of the drug in pregnant and lactating women and the effects of the drug on male and female fertility.
- (b) (4)

Drug Characteristics (b) (4) for Alkindi Sprinkle

Drug Class	Glucocorticoid
Mechanism of action	Glucocorticoids can cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.
Proposed Dosing and administration	-Dosage must be individualized. -Recommend oral administration of 8-10 mg/m2/day for patients with AI alone and 10-15 mg/m2/day in patients with congenital adrenal hyperplasia (CAH), typically in three or four divided doses. -The granules are contained in a capsule carrier which must not be swallowed but opened carefully. The granules are given directly into the mouth, and should not be chewed, but can be sprinkled onto soft food to assist dosing.
Molecular weight	362.5 g/mol

Metabolism	Following oral administration, hydrocortisone is rapidly absorbed from the gastro-intestinal tract. Hydrocortisone is metabolized in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol which are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.
Half-life	1.5 hours
Protein Binding	90% (corticosteroid-binding globulin and albumin)
Bioavailability	87%
Serious Adverse Reactions	May cause growth retardation in infancy, childhood and adolescence. Bone mineral density may be impacted in children when higher doses are used. Sudden withdrawal may cause adrenal crisis. Visual disturbance may be reported. Other adverse reactions include psychosis with hallucinations, delirium, mania, euphoria, gastritis, nausea, and hypokalemia.

Reviewer's table

Current State of the Labeling for the RLD Cortef (hydrocortisone) tablets

- Approved labeling is not in Physician Labeling Rule (PLR) or PLLR format.
- There is no boxed warning for this drug.
- There is a contraindication for use of Cortef in persons with systemic fungal infections and known hypersensitivity to components.

Usage in Pregnancy notes the following:

Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Corticosteroids have been shown to impair fertility in male rats.

- There are no existing pregnancy testing/contraception recommendations.
- There are no known drug-drug interactions with hormonal contraceptives.

REVIEW

PREGNANCY

Pregnancy and Adrenal Insufficiency

Adrenal insufficiency (AI) can be primary (Addison's disease) or secondary and tertiary due to disorders of the pituitary gland (corticotrophin [ACTH] secretion) or the hypothalamus (corticotropic-releasing hormone secretion). Primary AI is associated with both cortisol and mineralocorticoid deficiency. In contrast, secondary and tertiary AI are associated with cortisol, but not mineralocorticoid deficiency, because aldosterone is regulated primarily by the renin-angiotensin system, which is independent of the hypothalamus and pituitary. This distinction accounts for the different clinical presentations and management of these disorders.

Adrenal crisis may occur in acute AI, which is a life-threatening emergency that requires immediate treatment. Primary AI presents with volume depletion and hypotension due to

mineral corticoid deficiency. In those with secondary or tertiary AI, decreased vascular tone also leads to hypotension usually during acute stress. Biochemical features include hyperkalemia and hyponatremia. Current practice in North America and Europe favor the use of the short-acting glucocorticoid, hydrocortisone, for replacement therapy in both primary and secondary adrenal insufficiency.[1]

In those with nonclassical presentation of congenital adrenal hyperplasia, infertility is often present and associated with virilization. Pregnancy complicated by primary AI has been reported in about 100 women.[2] Before glucocorticoid replacement therapy became available, pregnancy in women with primary AI was associated with a maternal mortality rate as high as 35 to 45 percent and fetal growth restriction was common. At present, most women adequately treated for adrenal insufficiency go through pregnancy, labor, and delivery without difficulty, and babies achieve a normal birth weight.

Plasma cortisol levels rise during pregnancy due to an increase in cortisol-binding globulin (CBG). Free cortisol also rises during the 3rd trimester due to placental secretion of corticotropin releasing hormone (CRH) and an increase in the response to adrenocorticotropic hormone (ACTH). Current guidelines per the Endocrine Society recommend increasing hydrocortisone doses in pregnancy in AI patients, especially in the third trimester, and reviewing symptoms of hydrocortisone over-replacement and under-replacement at least per trimester. Hydrocortisone is preferred over cortisone acetate, prednisolone, or prednisone and recommended instead of dexamethasone because hydrocortisone is inactivated in the placenta. Hydrocortisone crosses the placenta, but placental 11 beta-dehydrogenase coverts hydrocortisone to cortisone, which is biologically inactive. Stress dose steroid is recommended in labor.[3] In labor, it has been suggested that the dose of hydrocortisone should be doubled. Adequate saline hydration and 25 mg hydrocortisone should be administered intravenously every six hours. At time of delivery, or if labor is prolonged, hydrocortisone should be administered IV in a dose of 100mg every six hours or as a continuous infusion. After delivery, the dose can be tapered rapidly to maintenance within three days.[3] Lactation is not a contraindication even though there is a possibility of a small level of transfer of hydrocortisone from maternal milk.[1]

Nonclinical Experience

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits without adrenal insufficiency have yielded an increased incidence of cleft palate in the offspring.

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[1] Castinetti F., Guignat L., Bouvattier C., Samara-Boustani D., Reznik Y. Group 4: Replacement therapy for adrenal insufficiency. Annales d'Endocrinologie 2017 78:6 (525-534)

[2] Nieman LK, Treatment of adrenal insufficiency in adults. UpToDate. https://www.uptodate.com/contents/treatment-of-adrenal-insufficiency-in-adults/print?search=adrenal%20insufficency&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3 Accessed 7/17/2020.

[3] Bornstein S, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. doi: 10.1210/jc.2015-1710.

The reader is referred to the full Pharmacology/Toxicology review by Fred Alavi, Ph.D. and Todd Bourcier, Ph.D.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published biomedical literature to determine if there is information concerning hydrocortisone use in pregnancy. One article of interest is listed below. For a full account of the applicant's review of literature in pregnancy, the reader is referred to the applicant's submission on July 30, 2020 under module 1.11 (Information not covered under modules 2 to 5, section 1.11.3.). The reader is referred to Appendix A to see the applicant's table of hydrocortisone use in pregnancy.

The applicant concluded:

> "Review of the literature on pregnancies treated with hydrocortisone suggests a miscarriage rate of 8.4% and major abnormality rate of 1% but this is likely to represent a publication bias for case reports of successful pregnancies. A large retrospective case survey from a national US births database suggests that women with [adrenal insufficiency] are more likely than the general population to deliver preterm, deliver by caesarean section, have impaired wound healing, develop infections and thromboembolism, require transfusions and have prolonged postpartum hospital admissions. Maternal mortality was significantly higher than in the comparison group. Congenital anomalies and small-for-gestational age infants were more likely in these pregnancies... Pregnancy in patients with adrenal insufficiency or congenital adrenal hyperplasia carries more risk than that in the general population due to their underlying disease and complications of that disease."

Reviewer comment:
The sponsor did not comment on the risk of orofacial clefts with the use of corticosteroids.

DPMH's Review of Literature

In 2016, DPMH completed a review of corticosteroids (including hydrocortisone) in pregnancy.[4] DPMH concluded that the available data from epidemiologic studies are contradictory regarding use of systemic corticosteroid during the first trimester of pregnancy in regard to orofacial clefts. Some studies showed an association with cleft lip with or without cleft palate, while more recent studies failed to confirm this association.

DPMH conducted an updated published literature review using Embase, Pubmed, Micromedex,[5] ReproTox,[6] Shepard's,[7] and TERIS.[8] Search terms used were "hydrocortisone AND pregnancy,"

[4] DPMH review of Pandel (hydrocortisone probutate) cream 0.1% NDA 20453 on December 8, 2016. DARRTS Reference ID 4025609
[5] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/20/2020.
[6] ReproTox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/20/2020.
[7] 2020 Shepard's: A Catalog of Teratogenic Agents, compilations of scientific reviews on the teratogenic effects of over 2000 drugs chemicals, and other physical and biologic agents. Accessed 7/20/2020.
[8] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 7/20/2020.

"hydrocortisone AND pregnancy AND fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage." There is one additional observational study on orally administered hydrocortisone use in pregnancy.

- Eyal O, et al.[9] conducted a retrospective observational study with 130 pregnancies among 59 women with biochemical and genetic diagnosis of Nonclassical 21-hydroxylase deficiency, of which 101 were treated with hydrocortisone, and 29 were not treated with hydrocortisone. The authors found there was no significant difference between the rate of miscarriages between treated and untreated pregnancies (17% vs. 25%, respectively, P=0.6). Birth weight was significantly lower in treated pregnancies compared to untreated pregnancies (2.9 ± 0.4 kg vs. 3.2 ± 0.5 kg, respectively, p=0.03). The authors published updated information in 2017,[10] this time including 187 pregnancies with nonclassical adrenal which resulted in 135 live births (130 singletons and 5 sets of twins), 7 elective terminations, 28 miscarriages (1st trimester), 3 ectopic pregnancies and 4 pregnancies that were ongoing during the study. There was a 20.3% miscarriage rate (excluding ectopic), which is higher than the rate of miscarriages (10.9%) in the general Israeli population. There was no significant difference between the rate of miscarriage in treated and untreated pregnancies. The time that it took to conceive with glucocorticoid therapy was similar to the time to conceive without it. However, the time to conceive with therapy was significantly shorter for the women who had failed to conceive without therapy. Birthweight adjusted for gestational age was similar in the treated and untreated pregnancies.

Most of the available published literature consists of studying corticosteroids as a class and their use in pregnancy. A recent article by Bandoli et al.[11] reviewed the published literature on corticosteroid use in pregnancy. The authors concluded:

> "The estimated risk of cleft lip with or without cleft palate from corticosteroid exposure has weakened over time, and no study published after 2003 has reported a statistically significant risk estimate... There may be a modest increase in the risk of cleft lip with or without palate from systemic corticosteroid use, but data are conflicting, and it is unknown to what extent maternal disease itself could contribute. There is little evidence that systemic corticosteroid use in pregnancy independently increases risks of preterm birth, low birth weight, or preeclampsia. Currently, there is not enough evidence to determine if systemic corticosteroid could contribute to gestational diabetes mellites."

The reader is referred to APPENDIX B for a list of major studies of corticosteroid use in pregnancy.

(b) (4)

[redacted]

(b) (4)

[9] Eyal O, et al. Pregnancy in women with nonclassic congenital adrenal hyperplasia: Time to conceive and outcome. Endocrine Abstracts (2015) 37 GP03.01 | DOI: 10.1530/endoabs.37.GP.03.01

[10] Eyal O, et al. Pregnancy in women with nonclassic congenital adrenal hyperplasia: Time to conceive and outcome. Clinical Endocrinology 2017; 87:552-556.

[11] Bandoli G, et al. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. Rheum Dis Clin North Am. 2017 August; 43(3): 489–502. doi:10.1016/j.rdc.2017.04.013

(b) (4)

(b) (4)

Shepard's[7] noted that in animal studies with various doses of hydrocortisone administered in mice, rats and rabbits, all doses produced cleft palate. According to Micromedex,[5] there are "no adequate or well-controlled studies of hydrocortisone sodium succinate use in pregnant women. Hydrocortisone is enzymatically inactivated in the placenta, thereby limiting fetal exposure. Hypoadrenalism may occur in infants born to women who are treated with corticosteroids during pregnancy." ReproTox[6] states that some "epidemiology studies have associated oral clefting with human pregnancy exposure to corticosteroids based on small numbers of affected children with exposures. Odds ratios in these reports were in the 3 to 5 range. One of the studies found an association only with topical steroids and not with oral steroids.[14] A review of human teratology studies on corticosteroids concluded that there was no evidence of an increase in malformations with these agents, but that a possible association with clefts could not be excluded."[15] TERIS[8] concludes the "therapeutic dose of hydrocortisone [is] unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk."

(b) (4)

[14] Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997; 56:335-40.
[15] Fraser FC, Sajoo A. Teratogenic potential of corticosteroids in humans. Teratology 1995; 51:45-6.

Reviewer comment:
This reviewer notes that the indication of Alkindi Sprinkle is for adrenal insufficiency, in which hydrocortisone is utilized as physiological replacement. The proposed dose of 8-15 mg/m^2 daily is much lower than the dose used for pharmacologic therapy. Both cortisol deficiency and cortisol excess has been associated with adverse pregnancy outcomes. Cortisol excess in pregnancy has been observed in Cushing disease, in which no increased risk of congenital defects was detected, but there was a high incidence of prematurity and other fetal and maternal complications.[6] Cortisol deficiency, as seen in those with adrenal insufficiency, has been associated with high maternal mortality. Therefore, cortisol replacement is necessary to maintain a healthy pregnancy.

Although animal studies suggest association of oral cleft (cleft lip with or without cleft palate) with hydrocortisone, available data from observational studies with hydrocortisone use in pregnant women as physiological replacement have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.[16,11] Again, use of physiological doses would not be expected to result in adverse outcomes because the doses used are much lower than doses used as pharmacologic therapy.

Overall, the applicant provided an adequate review of published literature regarding hydrocortisone use in pregnant women. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION
Nonclinical Experience
No animal lactation studies have been conducted with Alkindi Sprinkle.

The reader is referred to the full Pharmacology/Toxicology review by Fred Alavi, Ph.D. and Todd Bourcier, Ph.D.

Review of Literature
Applicant's Review of Literature
The applicant conducted an online search of published biomedical literature to determine if there is information concerning hydrocortisone use during lactation. Although there are serval articles on endogenous cortisol and lactation, there are none on administration of hydrocortisone in lactation. For a full account of the applicant's review of literature in lactation, the reader is referred to the applicant's submission on July 30, 2020 under module 1.11 (Information not covered under modules 2 to 5, section 1.11.3.).

The applicant concluded:

> "Cortisol is a physiological component of breastmilk that passes from the mother's bloodstream into milk... Maternal replacement dosing with hydrocortisone aims to reflect physiological cortisol secretion and so should approximate [physiologic amount of

[16] Bothou C, et al. Current Management and Outcome of Pregnancies in Women with Adrenal Insufficiency: Experience from a Multicenter Survey. The Journal of clinical endocrinology and metabolism 2020 105:8

cortisol in breastmilk]. However, cortisol has not been studied in breastmilk after exogenous administration of replacement doses of hydrocortisone... There is no data on exogenous hydrocortisone administration to lactating women and the effect on the breastfed child... substitution of hydrocortisone might be needed for adequate milk production."

DPMH's Review of Literature

DPMH conducted a published literature review using Embase, Pubmed, Micromedex,[17] ReproTox,[18] LactMed,[19] Hale,[20] and Briggs.[21] Search terms used in Embase and Pubmed were "hydrocortisone AND lactation," "hydrocortisone AND breastfeeding."

- No relevant articles were found on the use of exogenous hydrocortisone during breastfeeding.

According to LactMed,[19] "hydrocortisone (cortisol) is a normal component of breastmilk that passes from the mother's bloodstream into milk and might have a role in intestinal maturation, the intestinal microbiome, growth, body composition or neurodevelopment, but adequate studies are lacking. Concentrations follow a diurnal rhythm, with the highest concentrations in the morning at about 7:00 am and the lowest concentrations in the late afternoon and evening. Maternal stress can increase breastmilk cortisol levels." According to Briggs,[21] the amount of the corticosteroid in milk varies from 0.2 to 32 ng/mL with the highest mean concentrations (25.5 ng/mL) measured in colostrum during late pregnancy. The concentration of hydrocortisone in colostrum averages 7.5% of the plasma level. "Cortisol in milk may protect against later infant obesity, especially in girls."[21]

Hydrocortisone has not been studied in breastmilk after exogenous administration in pharmacologic amounts. There are no studies on the effects of hydrocortisone in the breastfed infants. Although there are no data on the effects of hydrocortisone on serum prolactin or on lactation, there is information on the effect of other glucocorticoid on lactation. According to ReproTox[18] and LactMed,[19] a study of 46 women who delivered an infant before 34 weeks of gestation found that a course of another corticosteroid (betamethasone, 2 intramuscular injections of 11.4 mg of betamethasone 24 hours apart) given between 3 and 9 days before delivery resulted in delayed lactogenesis II and lower average milk volumes during the 10 days after delivery. Milk volume was not affected if the infant was delivered less than 3 days or more than 10 days after the mother received the corticosteroid.[22] "An equivalent dosage regimen of

[17] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/21/2020.
[18] ReproTox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/21/2020.
[19] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The Lactmed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 7/21/2020.
[20] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.
[21] Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 7/21/2020.
[22] Henderson JJ, Hartmann PE, Newnham JP, Simmer K. Effect of preterm birth and antenatal corticosteroid treatment on lactogenesis II in women. Pediatrics. 2008;121: e92-100.

hydrocortisone might have the same effect."[19] In two case reports, depot corticosteroids in high doses were associated with a reversible cessation of lactation.[23,24] A study of 87 pregnant women found that betamethasone given as above during pregnancy caused a premature stimulation of lactose secretion during pregnancy. Although the increase was statistically significant, the clinical importance appears to be minimal.[25]

Micromedex[17] concludes "Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Based on the World Health Organization recommendation, hydrocortisone is compatible with breastfeeding in single dose use, but there is no data available regarding the prolonged use... Corticosteroids, when administered systemically, appear in human breast milk. In sufficient quantities, this could result in growth suppression, interfere with endogenous corticosteroid production, or cause other adverse events for the nursing infant." Both Hale[20] and Briggs[21] conclude that there are limited, or no data present and hydrocortisone is probably compatible with breastfeeding.

Reviewer comment:
Overall, the applicant provided an adequate review of published literature on the use of hydrocortisone during lactation. There are no data on the use of hydrocortisone during lactation. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No animal fertility studies have been conducted with Alkindi Sprinkle.

The reader is referred to the full Pharmacology/Toxicology review by Fred Alavi, Ph.D. and Todd Bourcier, Ph.D.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published biomedical literature to determine if hydrocortisone adversely affects fertility. A few of articles of interest are listed below. For a full account of the applicant's review of literature in lactation, the reader is referred to the applicant's submission on July 30, 2020 under module 1.11 (Information not covered under modules 2 to 5, section 1.11.3.).

- A case report of a 23-year-old male with bilateral testicular adrenal rest tumors (TART) and CAH with azoospermia. This patient was taking hydrocortisone. Azoospermia reversed when patient was switched from hydrocortisone to dexamethasone and the

[23] McGuire E. Sudden loss of milk supply following high-dose triamcinolone (Kenacort) injection. Breastfeed Rev. 2012 Mar;20(1):32-4. Review. PubMed PMID:22724311.
[24] Babwah TJ, Nunes P, Maharaj RG. An unexpected temporary suppression of lactation after a local corticosteroid injection for tenosynovitis. Eur J Gen Pract. 2013 Dec;19(4):248-50. doi: 10.3109/13814788.2013.805198. PMID: 24261425.
[25] Henderson JJ, Newnham JP, Simmer K, et al. Effects of antenatal corticosteroids on urinary markers of the initiation of lactation in pregnant women. Breastfeed Med. 2009; 4:201–6. PubMed PMID: 19772378.

partner became pregnant. The patient then switched back to hydrocortisone afterwards and the azoospermia returned. The patient switched to dexamethasone again to establish a second pregnancy, then switched back to hydrocortisone to avoid progressive weight gain and striae.[26]

- A cohort study of 15 male CAH patients, all of them on hydrocortisone. 3/15 patients with TART tried to father children, 0/3 succeeded; of 36 patients without TART, 7 of whom are married or living with a female partner, all of whom fathered 1 or more children.[27]
- A case report of a woman and her male partner who had failed 2 IVF cycles and were both diagnosed with nonclassical CAH subsequently. Within 40 days of hydrocortisone treatment of both partners, pregnancy occurred.[28]
- A cohort study consisted of 190 women with non-classical CAH, 99 pregnancies (52.9%) occurred before the diagnosis of nonclassical CAH (96 spontaneously and three with ovulation inducers) whereas 98 occurred after diagnosis (11 spontaneously and 77 with hydrocortisone treatment).[29]
- A total of 219 men with 21 hydroxylase deficiency with testicular sonography was performed in 164 men and sperm analysis was performed in 71 men. There were TARTS in 34% of 174 men. Severe oligospermia or azoospermia was found in 42% of patients and was more prevalent in men with TARTS (70%) than in men with normal testes. Among men living with female partners, TARTS were significantly more prevalent in those who had not fathered children. A survey of 104 men with CAH showed that 51% of the men who had a partner had at least one child, which is lower than the French reference population where 79% of adult males had fathered a child. The article did not specify how many men who had a partner were on hydrocortisone treatment.[30]
- A cohort study of 205 patients with CAH (128 women and 65 men in which 20% of women with classical CAH were treated with hydrocortisone, 16% of women with nonclassical CAH were treated with hydrocortisone, 37% of men with CAH were treated with hydrocortisone). 35% of women tried to get pregnant (classic, 25%; non-classic, 68%). 28 of 47 patients reported 46 live births, including 6 conceived after fertility treatment. The success rate of women with CAH seeking pregnancy was 54% in those

[26] Claahsen-van der Grinten HL, Otten BJ, Sweep FC, Hermus AR. Repeated successful induction of fertility after replacing hydrocortisone with dexamethasone in a patient with congenital adrenal hyperplasia and testicular adrenal rest tumors. Fertil Steril. 2007 Sep;88(3): 705.e5-8.

[27] Dumic M, Duspara V, Grubic Z, Oguic SK, Skrabic V, Kusec V. Testicular adrenal rest tumors in congenital adrenal hyperplasia-cross-sectional study of 51 Croatian male patients. Eur J Pediatr. 2017 Oct;176(10):1393-1404. doi: 10.1007/s00431-017-3008-7. Epub 2017 Sep 6. PMID: 28879515.

[28] Witchel SF. Management of CAH during pregnancy: optimizing outcomes. Curr Opin Endocrinol Diabetes Obes. 2012 Dec;19(6):489-96. doi: 10.1097/MED.0b013e32835a1a2e. PMID: 23108200.

[29] Bidet M, Bellanné-Chantelot C, Galand-Portier MB, Golmard JL, Tardy V, Morel Y, Clauin S, Coussieu C, Boudou P, Mowzowicz I, Bachelot A, Touraine P, Kuttenn , F. Fertility in women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2010 Mar;95(3):1182-90. doi: 10.1210/jc.2009-1383. Epub 2010 Jan 15. PMID: 20080854

[30] Bouvattier C, Esterle L, Renoult-Pierre P, de la Perrière AB, Illouz F, Kerlan V, Pascal-Vigneron V, Drui D, Christin-Maitre S, Galland F, Brue T, Reznik Y, Schillo F, Pinsard D, Piguel X, Chabrier G, Decoudier B, Emy P, Tauveron I, Raffin-Sanson ML, Bertherat J, Kuhn JM, Caron P, Cartigny M, Chabre O, Dewailly D, Morel Y, Touraine P, Tardy-Guidollet V, Young J. Clinical Outcome, Hormonal Status, Gonadotrope Axis, and Testicular Function in 219 Adult Men Born With Classic 21-Hydroxylase Deficiency. A French National Survey. J Clin Endocrinol Metab. 2015 Jun;100(6):2303-13.

with classic forms of CAH and 67% in those with non-classic forms of CAH. 24 of 65 men (37%) with female partners tried to achieve pregnancy, and 16 of 24 (67%) were successful, reporting 25 live births, including two conceived after fertility treatment.[31]

- Eyal et al.[32] conducted a retrospective study with 75 women diagnosed with nonclassical CAH. 72 women succeeded in conceiving (187) pregnancies. Time to conception was 4.0 +/- 7 months without and 3.3 +/- 3 months with glucocorticoid therapy (p =0.43). 17 pregnancies were achieved by glucocorticoid therapy after failure to conceive spontaneously. Time to conception before therapy initiation was 10.2 ± 11.4 months compared to 3.3 ± 3.4 months after therapy initiation (P = .02). Of 187 pregnancies, 135 (72%) resulted in live births, 38 (20.3%) ended in spontaneous miscarriages during the first trimester, seven (3.7%) were electively terminated, three (1.6%) were ectopic and four (2.1%) were ongoing during the study with similar rate in glucocorticoid treated and untreated pregnancies.
- A review article concludes that in females, some patients may require higher doses of glucocorticoids in order to adequately suppress adrenal androgen and progesterone secretion. In males, intensifying glucocorticoid treatment is the mainstay of medical therapy.[33]

The applicant concluded:

> "Patients with CAH exhibit ACTH driven androgen excess, which drives many aspects of the condition including male and female sub-fertility. Treatment with glucocorticoids, including hydrocortisone suppresses androgen excess."

Reviewer comment:
TARTs are thought to arise from aberrant adrenal cells in the testes that are stimulated by the chronically elevated ACTH, which is located in the mediastinum testes, leading to obstruction and congestion of the seminiferous tubules, which causes infertility. Another cause of gonadal dysfunction in male CAH patients may be suppression of the hypothalamic-pituitary-gonadal axis due to higher concentrations of adrenal androgens. Intensifying glucocorticoid therapy may lead to reduction of the tumor size by suppression of ACTH secretion, thereby improving testicular function. This is the case in the case report above. Infertility was related to CAH and tumor size and not due to hydrocortisone use.

DPMH's review of literature
DPMH conducted a review of published literature using Embase, Pubmed, Micromedex,[34] ReproTox[35] and TERIS.[36] Search terms used were "hydrocortisone AND reproduction,"

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[31] Arlt W, et al. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab. 2010 Nov;95(11):5110-21. doi: 10.1210/jc.2010-0917. Epub 2010 Aug 18. PMID: 20719839; PMCID: PMC3066446.
[32] Eyal O, et al. Pregnancy in women with nonclassic congenital adrenal hyperplasia: Time to conceive and outcome. Clinical Endocrinology. 2017; 87:552–556.
[33] Lekarev O, Lin-Su K, Vogiatzi MG. Endocrinol Metab Clin North Am. 2015 Dec;44(4):705-22. doi: 10.1016/j.ecl.2015.07.009. Epub 2015 Sep 1. PMID:
[34] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/21/2020
[35] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/21/2020.
[36] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 7/21/2020.

"hydrocortisone AND infertility," and "hydrocortisone AND contraception." Only one additional article was identified.

- Eyal O et al.[9] conducted a prospective controlled study with 130 pregnancies among 59 women with 21-hydroxylase deficient nonclassical adrenal hyperplasia and noted there was no difference in time to conception between pregnancies in women on treatment and those without treatment (7.7 ± 11 months vs. 7.5 ± 25 months).

Micromedex[34] states "animal reproductive toxicity studies indicate corticosteroids may impair male fertility.[37] However, fertility impairment and effect on mating performance was not observed in a fertility and reproductive study in males and females that were administered subQ hydrocortisone at doses up to 0.7 times the maximum therapeutic human dose."[38]

ReproTox[35] states "exercise-associated amenorrhea was attributed in the past to the elevation of serum cortisol concentrations produced by repeated strenuous activity,[39] although hypothalamic opioid action might be a more important mediator.

Guidance Labeling for combined Hormonal Contraceptives Draft published December 2017 states:

> "Concomitant use of [combined hormonal contraceptive] with thyroid hormone replacement therapy or corticosteroid replacement therapy may increase systemic exposure of thyroid-bind and cortisol-binding globin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased."

Reviewer comment:
This reviewer did not find any articles that suggest hydrocortisone adversely affects fertility.

Although co-administration with oral birth control pills may transiently interfere with the amount of cortisol that is bioavailable, the co-administration of both medications does not affect the efficacy of birth control pills. This reviewer recommends addressing this information under subsection 7 of the proposed product labeling. No addition to subsection 8.3 is warranted here.

Overall, the applicant provided an adequate review of published literature regarding hydrocortisone use in females and males of reproductive potential. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

The indication of Alkindi Sprinkle is physiologic replacement for adrenal insufficiency, in which the proposed dose is much lower than the dose used for pharmacologic therapy. Cortisol replacement is necessary to maintain a healthy pregnancy. The use of physiologic dose of

[37] Product Information: SOLU-CORTEF(R) intravenous injection, intramuscular injection, hydrocortisone sodium succinate intravenous injection, intramuscular injection. Pharmacia & Upjohn Co (per FDA), New York, NY, 2019.
[38] Product Information: LOCOID(R) topical lotion, hydrocortisone butyrate 0.1% topical lotion. Valeant Pharmaceuticals North America LLC (per FDA), Bridgewater, NJ, 2014.
[39] Ding J et al: High serum cortisol levels in exercise-associated amenorrhea. Ann Int Med 108:530-4, 1988.

hydrocortisone is not expected to cause major birth defects, miscarriage, and adverse maternal and fetal outcomes. Available data from observational studies with hydrocortisone use in pregnant women do not report a clear association with hydrocortisone and major birth defects, miscarriage or adverse maternal or fetal outcomes. No animal studies have been conducted for this NDA. Published animal studies have shown that administration of hydrocortisone and corticosteroid to pregnant animals can cause abnormalities of fetal development including cleft palate, intrauterine growth retardation and effects on brain growth and development. However, the use of hydrocortisone in animal studies was not done in the setting of physiologic replacement as is indicated for Alkindi Sprinkle.

Additionally, there are risks to the mother associated with untreated adrenal insufficiency in pregnancy, including maternal death, and risk of hypoadrenalism in infants exposed to substantial doses of corticosteroids in pregnancy. (b) (4)

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 postmarking pregnancy safety study at the current time.

Lactation

The indication of Alkindi Sprinkle is physiologic replacement for adrenal insufficiency; therefore, administration of Alkindi Sprinkle is not expected to adversely affect the breastfed infant or milk production. Cortisol is present in human breast milk endogenously. There are no data on the presence of exogenously administered hydrocortisone in human milk, the effects on the breastfed infant, or the effects on milk production. Based on this information, DPMH recommends using the standard risk/benefit statement in section 8.2 of labeling.

The use of hydrocortisone at a physiologic dose for adrenal insufficiency is not expected to adversely affect the breastfed infant or milk production. DPMH does not recommend a clinical lactation study at the current time.

Females and Males of Reproductive Potential

CAH cause infertility. Available data from published literature have not identified any adverse effects on fertility when hydrocortisone was utilized as a hormone replacement in females and males of reproductive potential. Published animal fertility studies indicate corticosteroids may impair male fertility, however, that was not used as hormone replacement.

Although estrogen containing birth controls may affect the amount of free cortisol available by increase serum concentration of CBG transiently, the co-administration of both medications does not affect the efficacy of birth control pills. DPMH recommends addressing this drug to drug interaction under subsection 7 of the labeling. DPMH recommends omitting subsection 8.3.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH recommendations are below and reflect the discussions with Division of General Endocrinology. DPMH refers to the final NDA action for final labeling.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

APPENDIX A. Applicant's Table of Hydrocortisone Use in Pregnancy

Paper	Type	Population	Hydrocortisone Dose	Pregnancy outcomes	Notes
Schneiderman et al. 2016	Survey	AI	N/A	Compared Addisons to normal population births in the United States' Healthcare Cost and Utilization Project-Nationwide Inpatient Sample from 2003 to 2011. Compared with women without AD, women with AD were more likely to deliver preterm (OR 1.50, 95% CI 1.16–1.95), deliver by caesarean section (OR 1.32, 95% CI 1.08–1.61), have impaired wound healing (OR 4.28, 95% CI 2.55–7.18), develop infections (OR 2.44, 95% CI 1.66–3.58) and develop thromboembolism (OR 5.21, 95% CI 2.15–12.63), require transfusions (OR 6.69, 95% CI 4.69–9.54), and have prolonged postpartum hospital admissions (OR 5.71, 95% CI 4.37–7.47). Maternal mortality was significantly higher than in the comparison group (OR 22.30, 95% CI 6.82–72.96). Congenital anomalies (OR 3.62, 95% CI 2.05–6.39) and small-for-gestational	ICD9 code used is for adrenal insufficiency and not CAH Glucocorticoid replacement type not stated

Paper	Type	Population	Hydrocortisone Dose	Pregnancy outcomes	Notes
				age infants (OR 1.78, 95% CI 1.15–2.75) were more likely in these pregnancies	
Mastrogiannis et al. 1994 USA Greece	Review	AI	N/A	Describes series of 5 women with 6 normal live births	Notes cleft palate findings in rodents not seen in humans
Lo et al 2001 USA	Review	CAH	N/A	Describes 105 pregnancies in 73 women with CAH 11 miscarriages 11 therapeutic abortion 1 ectopic 74 live births 8 pregnancy outcomes not known	Recommends using a glucocorticoid s metabolized by placental 11βHSD2 such as Hydrocortisone, cortisone acetate, prednisone, prednisolone, and methylprednisolone to reduce fetal exposure
Fux Otta et al. 2008 Argentina	Case series	AI	30mg	Describes 3 pregnancies 1 normal term delivery 1 neonatal RDS survived NICU 1 mother stopped hydrocortisone LBW neonate with RDS died	
Bensing et al 2020 Sweden Germany USA	Review	AI	N/A	Summarises several case series: Sweden: n=1188 Reduced fecundity after diagnosis Most outcomes NVD and no increase in congenital anomalies but increased risk of CS (OR 2.35; 95% CI 1.68–3.27) and premature labour (OR 2.61; 95% CI 1.69–4.05)	Suggests some risk of preterm delivery may be due to non-compliance with or inadequate replacement therapy

Paper	Type	Population	Hydrocortisone Dose	Pregnancy outcomes	Notes
				Germany: N=56 Higher risk of CS but not premature labour USA: N=552 Higher risk of CS (OR 1.32; 95% CI 1.08–1.61) and premature labour (OR 1.50; 95% CI 1.16–1.95) Increased frequency of postpartum complications increased maternal mortality (3 deaths)(OR 22.30; 95% CI 6.82–72.96). risk of impaired fetal growth and congenital anomalies	
Bothou et al 2020 USA, UK, Germany, Italy, Sweden, Denmark, Switzerland	Survey	CAH (25%)/AI	21.6-27.4mg	Surveyed 128 pregnancies in 113 women 21.4% premature delivery 58% CS 3 miscarriages 2 preterm infants required NICU 1 shoulder dystocia 12.5% maternal complications No maternal or fetal deaths	
Hatabu et al., 2019 Japan	Case series	Lipoid Congenital Adrenal Hyperplasia	N/A	2 pregnancies with normal outcome in 2 women. Glucocorticoid replacement type not specified	
Remde et al. 2016	Survey	CAH and AI	20-22.5mg	25 pregnancies in CAH patients 9 miscarriages	No congenital anomalies reported in the study

Paper	Type	Population	Hydrocortisone Dose	Pregnancy outcomes	Notes
Germany				1 therapeutic abortion 15 live births 46% CS 1/3 small for gestational age 93 pregnancies in Addison patients 11 miscarriages 9 therapeutic abortions 73 live births 13% CS	CS rate in CAH partially due to genital complications of disease Study reported in Bensing above
Albarel et al. 2016 France	Case report	Lipoid CAH	30-90mg	Successful pregnancy and outcome	
Reisch 2019 Germany	Review	CAH	N/A	Reviews practice and case series of pregnancy in CAH Overall reports 169 pregnancies with 128 live births, 14 miscarriages and 21 therapeutic abortions	Considers overall outcomes in CAH pregnancies good Recommends prednisolone or hydrocortisone replacement during pregnancy
Witchel 2012 USA	Review	CAH	N/A		Recommends Hydrocortisone or prednisone/prednisolone replacement due to 11βHSD2 inactivation by placenta
Purwana et al. 2013 Japan	Case study	Non-classic CAH	20mg	Normal pregnancy and delivery	

Paper	Type	Population	Hydrocortisone Dose	Pregnancy outcomes	Notes
Kamata et al. 2011 Japan	Case study	CAH	10mg	Normal delivery and neonate	Mucinous cystadenoma diagnosed and removed during gestation
Trakkakis et al. 2011 Greece	Case study	Non-classic CAH	25mg	Normal pregnancy and delivery	Both parents and child had non-classic CAH
Bidet et al 2010 France	Case series	Non-classic CAH	20-25mg	52 pregnancies with hydrocortisone supplementation and 10 with dexamethasone resulted in five miscarriages (6.5%), two voluntary abortions (2.5%) and 73 live births	Reported marked difference in miscarriage rate between untreated and glucocorticoid treated pregnancies (25.2 *vs.* 4.8%) Recommended hydrocortisone as therapy in pregnancy
Hagenfeldt et al. 2008 Sweden	Survey	CAH	30-40mg	Describes 31 pregnancies in 16 women but only 2 in a hydrocortisone treated woman	Normal outcome
Arlt et al. 2007 UK	Review	CAH	N/A	Describes treatment of pregnancy in CAH	Recommends hydrocortisone or prednisolone due to placental 11βHSD2 inactivation of cortisol. Recommends increasing glucocorticoid dose in third trimester
Mains et al. 2007 USA	Case report	Non-classic CAH	25-35mg	Case switched to hydrocortisone from dexamethasone at 10 weeks gestation.	

Paper	Type	Population	Hydrocortisone Dose	Pregnancy outcomes	Notes
				Hirsutism in pregnancy. Live normal twins born by CS	
Moran et al 2006 USA Mexico Israel France Brazil Portugal Italy Spain	Survey	Non-classic CAH	10-20mg	16 pregnancies with glucocorticoids in gestation (3 hydrocortisone) 0 miscarriages and 81.3% live births	
Dumic et al 2005	Case series	CAH	25mg	4 pregnancies in 4 CAH patients (1 treated with Hydrocortisone) Normal infant delivered by elective CS	
Hoepfner et al. 2004 Germany	Case series	CAH	13.6-24.2mg/m^2/day	9 pregnancies in 6 CAH patients. All treated with hydrocortisone. 1 miscarriage and 8 normal infants.	
White and Speiser 2002 USA	Review	CAH	N/A	Recommends using hydrocortisone or prednisolone in pregnancy	
Krone 2001 Germany	Survey	CAH	22.5-40mg	Review of 18 CAH patients with a viable newborn. 7 pregnancies treated with hydrocortisone. 4/7 CS. One male born SGA with intracerebral bleed, but normal outcome attending mainstream school.	

Paper	Type	Population	Hydrocortisone Dose	Pregnancy outcomes	Notes
Jääskeläinen et al 2000 Finland		CAH	20-60mg	13 pregnancies in 9 patients. 2 miscarriages 1 therapeutic abortion 10 normal infants (7 delivered by CS) 4 delivered after pregnancies with hydrocortisone replacement	
Zacharin 1999 Australia	Case study	CAH	30-48mg	Case study of CAH patient pregnancy treated with hydrocortisone. Gestational diabetes at 31/40. CS was covered with 2x 100mg iv hydrocortisone. Neonatal hypoglycaemia prompted diagnosis of adrenal suppression. Rapid resolution and discharged day 7	Suggests careful monitoring for adrenal suppression in infants of CAH mothers.
Lo et al. 1999 USA	Case series	CAH	37.5mg (cortisone)	4 pregnancies in CAH patients.one patient treated with cortisone acetate. Normal vaginal delivery of healthy infant.	Recommends using Cortisone, hydrocortisone, prednisolone or prednisone in pregnancy due to 11βHSD2 activity of placenta.
Owa et al 2017 Japan	Case Review	SLE	143-234mg intravenously	Review of high dose or low dose steroid supplementation in labour. 55 women with low dose and 47 with high dose steroids. There were no differences between groups in pregnancy outcomes. CS was 21-28%	
Boelig et al 2016 UK	Cochrane review	Hyperemesis Gravidarum	300mg intravenously	Reviewed treatments for hyperemesis including hydrocortisone and other corticosteroids. Hydrocortisone reduced emesis rates, but no other outcomes were available. Corticosteroid treated pregnancies did not differ from those with placebo for	

Paper	Type	Population	Hydrocortisone Dose	Pregnancy outcomes	Notes
				pregnancy complications, spontaneous abortion, stillbirth and congenital Abnormalities.	
Adonakis et al. 2005 Greece	Case report	AI	30-60mg	Case report of pregnancy in Addison patient. Normal pregnancy and delivery of normal infant	
Stechova 2004 Czech Republic	Case Report	APS type 2	30-37.5mg	Case report of patient with APS type 2 (Addison's Thyroid disease and type 1 diabetes) treated with hydrocortisone and insulin in pregnancy. Transient pre-eclampsia and elective CS at 37/40. Neonate with macrosomia and hypoglycaemia, hypocalcaemia and tachypnoea. Diagnosed with adrenal suppression and treated with hydrocortisone for one week. Recovered and discharged.	
Volz et al. 2002 Germany	Case report	Hypopituitarism	N/A	Patient with hypopituitarism treated with cortisol [sic}. Uncomplicated pregnancy and delivery of healthy infant.	
Nelson-Piercy et al. 2001 UK	Clinical trial	Hyperemesis Gravidarum	200mg iv	Trial of placebo versus prednisolone followed by iv hydrocortisone for hyperemesis. 25 women (24 randomised), 3 treated with hydrocortisone. Pregnancy outcomes similar between steroid and placebo group, 1 neonatal death from preterm delivery, 10 normal infants and 1 patient lost to follow up.	

APPENDIX B. Major Studies of Corticosteroid use in Pregnancy

Publication	Type	N (exposed)/drug/disease	Timing	Exposure	Outcome	Comments (Strengths (S) /Limits (L))
Bandoli G, et al.[40] (2017) USA	Review article	corticosteroid			-The estimated risk of cleft lip with or without cleft palate from corticosteroid exposure has weakened over time, and no study published after 2003 has reported a statistically significant risk estimate. -There is little evidence that systemic corticosteroid use in pregnancy independently increases risks of preterm birth, low birth weight, or preeclampsia. Currently, there is not enough evidence to determine whether systemic corticosteroids could contribute to gestational diabetes mellitus.	
Skuladottir H, et al.[41] (2014) USA	Case controlled population-based study	1577 infant with cleft lip and 795 infants with cleft palate only with 5922 controls corticosteroid	12 weeks before and all though pregnancy	Data from National Birth Defect Prevention Study (1997-2002) and (2003-2009)	- A previous report from the National Birth Defect Prevention Study (NBDPS), using data from 1997 to 2002, found an association with cleft lip and palate (odds ratio, 1.7; 95% confidence interval [CI], 1.1-2.6), but not cleft palate only (odds ratio, 0.5, 95%CI, 0.2-1.3). -current study with larger sample size found overall association of corticosteroids and cleft lip and palate in the new data was 1.0 (95% CI, 0.7-1.4). There was little evidence of associations between specific corticosteroid components or timing and clefts.	S-large sample size; adjusted for race, education, intake of folic acid supplement, smoking, study center. L- recall bias (mothers were interviewed to see if corticosteroid was used and what was the medical diagnosis); disease was not taken into consideration; dose and whether or not the women actually took the medication was not taken into consideration.
Hviid A, et al.[42] (2011) Denmark	Case controlled population-	1232 oral cleft (84 were exposed to corticosteroids in the 1st trimester)	3 weeks before and all pregnancy, 1st trimester	Data from Denmark from 1996-2008 (n=832, 636) and 51973 exposures (1st trimester).	-No statistically significant increased risk of orofacial clefts associated with the use of corticosteroids: cleft lip with or without cleft palate, prevalence odds ratio (OR) 1.05 (95% confidence interval [CI] 0.80-1.38]; cleft palate alone, prevalence OR 1.23 (95% CI 0.83-1.82).	S-large sample size; adjusted for socioeconomic status, smoking, family history, maternal disease (infection, diabetes, epilepsy, other medications)

[40] Bandoli G, et al. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. Rheum Dis Clin North Am. 2017 August; 43(3): 489–502. doi:10.1016/j rdc.2017.04.013

[41] Skuladottir H, Wilcox AJ, Ma C, et al. Corticosteroid use and risk of orofacial clefts. Birth Defects Res Part A - Clin Mol Teratol. 2014; 100(6):499–506. DOI: 10.1002/bdra.23248

[42] Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. C Can Med Assoc J. 2011; 183(7):796–804. DOI: 10.1503/cmaj.101063

	based study	corticosteroid (oral, inhaled, nasal, topical)			- OR for cleft lip with or without cleft palate associated with the use of dermatologic corticosteroids was 1.45 (95% CI 1.03-2.05). For hydrocortisone aOR for cleft lip with 1st trimester is 1.28 (95% Ci 0.41-2.98) and 1.02 (95% CI 0.14-7.23) for cleft palate alone.	L- claims-based database and disease was not taken into consideration; claim based database-uncertain if women actually took the medication
Bay Bjorn A-M, et al.[43] (2014) Denmark	population-based cohort study literature review	1449 exposed corticosteroid (inhaled or oral)	30 days before and 1st trimester	Data from primiparous women in northern Denmark from 1999-2009 (n=83,043) with 1449 used corticosteroid. A literature review of corticosteroid use in pregnancy in the last 25 years.	-Oral cleft in the offspring was recorded for 1 of the users (0.08%) and 145 of the nonusers (0.2%), prevalence odds ratio (OR) 0.47 [95% confidence interval (CI), 0.07-3.34]. The prevalence OR for congenital malformations overall was 1.02 (95% CI, 0.79-1.32). -10 studies on the association between corticosteroid use in early pregnancy and congenital malformation overall or oral clefts with overall relative estimates ranging from 0.8 (95% CI, 0.4-1.7) to 2.1 (95% CI, 0.5-9.6). For oral clefts (including cleft lip with or without cleft palate and isolated cleft palate, OR ranged 0.6 (95% CI, 0.2-1.7) to 5.2 (95% Ci, 1.5-17.1)	S-large sample size; adjusted for smoking, age, diabetes L-disease was not taken into consideration; claims-based database-uncertain if women actually took the medication
Pradat P, et al.[44] (2003) Multi-countries	population-based case-controlled study	11,150 infants with any malformation corticosteroid (oral, inhaled, topical)	1st trimester	Data from MADRE project (1990-2002) consists of 11,150 cases of congenital malformations with positive exposures in the first trimester.	A slight association is observed between exposure to corticosteroids for systemic use and the occurrence of cleft lip with or without cleft palate (OR, 2.59; 95% CI, 1.18-5.67).	S-several routes of administration were evaluated L-disease was not taken into consideration, database study without consideration for dose and frequency;
Carmichael SL, et al.[45] (2007) USA	population-based case-controlled study	1141 infants with orofacial cleft corticosteroid	4 weeks before and 1st trimester	Data from National Birth Defect Prevention Study (1997-2002). Mothers of 33 infants with cleft lip ± cleft palate (CLP) (2.9%), mothers of 6 infants with cleft palate (CP) (1.0%), and 72 control subjects (1.7%) reported corticosteroid use.	The crude odds ratio for "any" vs "no" use was 1.7 (95% CI, 1.1-2.6) for CLP and 0.5 (0.2-1.3) for CP. When analyzed by route of administration and medication components, odds ratios for cleft lip with or without cleft palate tended to be elevated, and odds ratios for CP tended to be close to 1.	S-large sample size; adjusted for covariant: race, education, intake of folic acid, smoking, study center. L- disease was not taken into consideration; dose and whether or not the women actually took the medication was not taken into consideration.

[43] Bay Bjorn A-M, Ehrenstein V, Hundborg HH, Nohr EA, Sorensen HT, Norgaard M. Use of corticosteroids in early pregnancy is not associated with risk of oral clefts and other congenital malformations in offspring. Am J Ther. 2014; 21(2):73–80. DOI: 10.1097/MJT. 0b013e3182491e02 [PubMed: 23011170]
[44] Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P, Contributors to the MADRE database. First trimester exposure to corticosteroids and oral clefts. Birth Defects Res A Clin Mol Teratol. 2003; 67:968-70.
[45] Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007; 197:585.e1-585.e7.

Kallen B, et al.[46] (2003) Sweden	population-based case-controlled study	1142 infants with orofacial cleft corticosteroid (systemic, topical, nose drip, inhaled)	1st trimester	Data from Swedish Birth Registry (1995-2001) with 576,873 births and 1044 with orofacial clefts and no known chromosomal anomaly.	-An association between glucocorticoid use and infant cleft was indicated and seemed to be strongest for median cleft palate. With all types of exposures together there is OR 1.43. - Any drug use was not associated with clefts (odds ratio [OR] = 0.98, 95% confidence interval [95% CI] = 0.85 to 1.13), with isolated clefts (OR = 0.92) with isolated median cleft palate (OR = 1.03, 95% CI = 0.79 to 1.36) or with isolated cleft lip with or without cleft palate (OR = 0.86, 95% CI = 0.71 to 1.05).	S-Large sample size, adjusted for year of birth, maternal age, parity, smoking L-not adjusted for other drugs or disease; unadjusted for drugs' dose and if the women actually took the medication.
Edwards MJ, et al.[47] (2003) Australia	Case controlled	48 children corticosteroid (systemic)	1st trimester	A case-control survey of 48 children with nonsyndromic cleft lip or palate showed a significant increase in prevalence of maternal use of topical corticosteroid preparations in the first trimester of pregnancy, compared to 58 controls born in the same hospital.	Odds ratio for nonsyndromic cleft lip or palate was 13.154, 95% confidence interval 1.67-586, P = 0.0049 on Fisher's exact two-tail test.	S- adjusted for covariates: income, family history of cleft, age, birth length and order. L-Small sample size; retrospective and suspect to recall bias
Rodriguez-Paneilla E, et al.[48] (1998) Spain	Case controlled population-based study	1184 infants any systemic corticosteroid	1st trimester	Data from Spanish Collaborative study of congenital Malformations (ECEMC) with 1184 infants with non-syndromic oral clefts vs matched controls.	There is an increased risk of cleft lip (with or without cleft palate) in the newborn infants (OR = 6.55; CI = 1.44-29.76; P = 0.015),	S-controlled for potential confounding factors, such as maternal smoking, maternal hyperthermia, first-degree malformed relatives with cleft lip with or without cleft palate, and maternal treatment with antiepileptics, benzodiazepines, metronidazole, or sex hormones during the first trimester of pregnancy L-chart based, heterogenous population of various degrees of exposure to various corticosteroids (dose not assessed)

[46] Kallen B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. Cleft Palate Craniofac J. 2003 Nov;40(6):624-8.
[47] Edwards MJ, Agho K, Attia J, Diaz P, Hayes T, Illingworth A, Roddick LG. Case-control study of cleft lip or palate after maternal use of topical corticosteroids during pregnancy. Am J Med Genet A. 2003; 120:459-63.
[48] Rodriguez-Panilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: A case-control study. Teratology 1998; 58:2-5.

Robert E, et al.[49] (1994) Multi-country	Populated based case control study	1448 cases corticosteroid	1st trimester	Data from the International Clearinghouse for Birth Defect Monitoring Systems is named MADRE: MAlformation DRug Exposure surveillance to evaluate 1st trimester drug exposure with malformations from 1990-91, yielded 1448 infants with malformation with drug exposures.	7 infants with facial clefts were reported as exposed to corticosteroids (OR 3.16; 95% CI 1.08-7.91; P= 0.04). All were cleft lip, with or without cleft palate.	L-dose and disease was not assessed
Carmichael SL,[50] (1999) USA	population based case-control study	662 infants with oral cleft corticosteroid	1 month before and 1st trimester	Data from California Birth Defects Monitoring Program (1987-88) with 344,214 infants, with cases of orofacial clefts (n = 662), conotruncal heart defects (n = 207), neural tube defects (n = 265), and limb reduction defects (n = 165). Information on medication use was collected via maternal telephone interviews.	Corticosteroid use was associated with an increased risk for isolated cleft lip with or without cleft palate (odds ratio 4.3, 95% confidence interval 1.1-17.2) and isolated cleft palate (odds ratio 5.3, 95% confidence interval 1.1-26.5). Increased risks were not observed for the other anomaly groups studied.	S- large database L-recall bias; timing/mode/dose of exposure was not assessed
Park-Wyllie L, et al. [51] (2000) Canada	prospective controlled Meta-analysis	184 exposed prednisone (systemic) corticosteroid	1st trimester	184 women exposed to prednisone in pregnancy and 188 pregnant women who were counseled by Motherisk for nonteratogenic exposure A meta-analysis of all epidemiological studies was conducted.	No statistical difference in the rate of major anomalies between the prednisone-exposed and control groups. (3.6% vs 2% control) In the meta-analysis, the Mantel-Haenszel summary odds ratio for major malformations with all cohort studies was 1.45 [95% CI 0.80, 2.60] and 3.03 [95% CI 1.08, 8. 54] when Heinonen et al. ('77) was removed. There is a marginally increased risk of major malformations after first-trimester	S- prospective L-small sample size

[49] Robert E, Vollset SE, Botto L, Lancaster PAL, Merlob P, Cocchi G, Ashizawa M, Sakamoto S, Orioli I. Malformation surveillance and maternal drug exposure: the MADRE project. Rick Safety Med 1994; 6:78-118.
[50] Carmichael SL; Shaw GM: Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999; 86:242-4.
[51] Park-Wyllie L, Mazzotta P, Pastuszak A et al: Birth defects after maternal exposure to corticosteroids: Prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000; 62:385-392.

					exposure to corticosteroids. In addition, summary odds ratio for case-control studies examining oral clefts was significant (3.35 [95% CI 1.97, 5.69]).	
Czeizel AE, et al.[52] (1997) Hungary	population based case-control study	20830 cases and 35727 control Corticosteroid (systemic, ointment, and spray)	All	Data from Hungarian Case-Control Surveillance of Congenital Abnormalities (1980-1994) including 20,830 cases and 35,727 controls. Corticosteroid tablet pregnancy exposure was 1.55% among 20,830 malformed cases and 1.41% among 35,727 healthy control births (P = 0.2).	Corticosteroid tablet pregnancy exposure was 1.55% among 20,830 malformed cases and 1.41% among 35,727 healthy control births (P = 0.2). Corticosteroid ointment pregnancy exposure was 0.35% among malformed and 0.33% among control births (P = 0.7). The absolute risk of oral and ointment corticosteroid treatment was low in pregnancy and in the critical period for major congenital abnormalities.	S-large sample size; adjusted for age, birth order, proportion of threatened abortion and preterm labor, maternal disorders, other-drug use. L-comedications not assessed, disease not considered
Norgard B, et al.[53] (2007) Denmark	population based cased controlled study	900 children corticosteroid Crohn's disease	30 days before and all pregnancy	A nationwide Danish cohort study of 900 children born to CD women between 1996 and 2004, drugs such as 5-ASA and steroids (local or systemic) or AZA.6-MP assessed	Among steroid exposed, the risk of preterm birth was 1.4 (95% CI 0.6-3.3), with "disease activity" as major confounder. There is no increased risk of low birth weight (LBW) at term or congenital anomalies (CA).	S- large sample size L-disease severity was not taken into consideration; claim based and unclear if the women took the drug; drug dose and frequency was not taken into consideration.
De Man YA, et al.[54] (2009)	prospective study	152 prednisone RA	All	152 Caucasian RA patients with singleton pregnancies were evaluated before conception (when possible), during each trimester of the pregnancy, and postpartum. Clinical characteristics, disease activity, medication use, and pregnancy outcome were analyzed.	No association with LBW. Disease activity was associated with LBW (P = 0.025). The gestational age at delivery was significantly lower in women who were taking prednisone (38.8 versus 39.9 weeks; P = 0.001), and their delivery was more often premature (<37 weeks; P = 0.004).	S- prospective, adjusted for disease activity medication, gestational age. L- small sample size

[52] Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997; 56:335-40.
[53] Nørgård B, Pedersen L, Christensen L a, Sørensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. Am J Gastroenterol. 2007; 102(7):1406–1413. DOI: 10.1111/j.1572-0241.2007.01216.x [PubMed: 17437503]
[54] De Man YA, Hazes JMW, Van Der Heide H, et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: Results of a national prospective study. Arthritis Rheum. 2009; 60(11):3196–3206. DOI: 10.1002/art.24914 [PubMed: 19877045]

Al Arfaj As, et al.[55] (2010) Saudi Arabia	Retrospective	396 SLE		319 women with SLE planning pregnancy after SLE onset, 176 (55.2%) conceived resulting in 396 pregnancies. Pregnancy outcomes assessed.	Prednisone supplementation in pregnancy is associated with IUGR with wide CI crossing 1.	
Magee LA, et al.[56] (2002) Canada	review				Risk for MCM was not significant in pooled data from cohort studies on use of corticosteroids in pregnancy (relative risk:1.24; 95% confidence interval: 0.97-1.60). Similar results were seen when data from case-control studies was analyzed (relative risk: 1.20; 95% confidence interval: 0.93-1.56). A small, but significant increase in cleft palate (relative risk 3.19; 95% confidence interval: 0.93-1.56) was seen in pooled data from case-control studies examining the rate of malformation with corticosteroid use.	
Willoughby CP, et al.[57] (1980) UK	Retrospective cohort	156 women topical and/or systemic corticosteroid	All	A 20-year survey (1960-79) of 156 pregnant women with active ulcerative colitis who were treated with corticosteroids alone (topical or systemic), corticosteroids with sulfasalazine, or undetermined regimens. There were 104 total pregnancies.	-There were 3 cases of congenital abnormalities and 2 cases of cerebral palsy (CP) both were born prematurely (1 had congenital dislocation of the hips and 2 had hypospadias) -11 cases of SAB (2/31 no treatment; 1/22 sulphasalazine; 2/13 topical steroid; 1/15 sulphasalazine +topical steroid; 5/15 in sulphasalazine + systemic and topical steroid). Author suggest the higher SAB rate in the combination group maybe due to disease severity. -overall SAB and MCM rate are same as the background population. -The incidence of low-birth weight infants was the same in the steroid and nonsteroidal treated groups.	S-disease activity was taken into consideration L-small sample size
Mogadam M, et al.[58] (1981) USA	Retrospective cohort	531 pregnancies	all	Two hundred eighty-seven pregnancies (172 ulcerative colitis and 115 Crohn's disease) were treated with either sulfasalazine or	-The use of corticosteroid and sulfasalazine in pregnancy associated with ulcerative colitis is unlikely to increase the fetal morbidity or mortality. -Patients with severe Crohn's disease requiring corticosteroid and/or both drugs experienced more complications than the	L-retrospective and not checked against a chart subjective to recall biased; disease severity was not accounted for; not randomized

[55] Al Arfaj AS, Khalil N. Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. Lupus. 2010; 19(14):1665–1673. DOI: 10.1177/0961203310378669 [PubMed: 20947541]
[56] Magee LA, Mazzotta P, & Koren G: Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). Am J Obstet Gynecol 2002; 186: S256-261.
[57] Willoughby CP & Truelove SC: Ulcerative colitis and pregnancy. Gut 1980; 21:469-474.
[58] Mogadam M, Dobbins WO, Korelitz BI, et al: Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. Gastroenterology 1981; 80(1):72-76.

				corticosteroids or both drugs, whereas 244 (137 ulcerative colitis and 107 Crohn's disease) received neither.	"untreated" ones, but still fewer than the prevailing rates in the general pregnant population. The higher complication rate seems to be associated more with disease-related factors than the use of these drugs. -In the management of inflammatory bowel disease associated with pregnancy, either or both drugs may be used just as in the nonpregnant patients.	
Reinisch JM, et al.[59] (1978)	retrospective	119 pregnancy exposed prednisone	all	119 pregnancy exposed to prednisone 10mg orally daily for infertility and throughout pregnancy compared to 67 controls.	Offspring exposed to prednisone weighed significantly less than control ($p < 0.0001$). No congenital anomalies were noted.	L-small sample size; it is also unclear what was the real cause of infertility and why some where given prednisone and others did not.

CA: congenital anomaly; CP: cerebral palsy; SAB: spontaneous miscarriage; AZA: azathioprine; 6-MP: mercaptopurine; LBW: low birth weight

[59] Reinisch JM, et al. Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science 1978; 202 (4366): 436-438. DOI: 10.1126/science.705336

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/s/

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08/25/2020 12:20:56 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 17, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 213876
Product Name and Strength:	Alkindi Sprinkle (hydrocortisone) oral granules, 0.5 mg, 1 mg, 2 mg and 5 mg per capsule
Applicant/Sponsor Name:	Diurnal
OSE RCM #:	2019-2455-1
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 30, 2020 and August 10, 2020 for Alkindi Sprinkle. The Division of General Endocrinology requested that we review the revised container labels and carton labeling for Alkindi Sprinkle (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations we made during a previous label and labeling review[a] and feedback provided by the Office of Product Quality related to storage and dosage form presentation.

2 CONCLUSION

The revised container labels and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Fanari, M. Label and Labeling Review for Alkindi Sprinkle (NDA 213876). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jul 15. RCM No.: 2019-2455 2019-2510.

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/s/

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08/17/2020 01:16:47 PM

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 15, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 213876
Product Name, Dosage Form, and Strength:	Alkindi Sprinkle (hydrocortisone) oral granules, 0.5 mg, 1 mg, 2 mg and 5 mg per capsule
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Diurnal
FDA Received Date:	November 29, 2019 and May 28, 2020
OSE RCM #:	2019-2455 2019-2510
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

As part of the 505(b)(2) NDA for Alkindi Sprinkle (hydrocortisone) capsule, the Division of General Endocrinology (DGE) requested that we review the proposed Alkindi Sprinkle Prescribing Information (PI), Medication Guide (MG), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 Regulatory History

Diurnal proposes to market Alkindi Sprinkle as a multi-particulate granule formulation stored in hard capsules as the storage medium and the capsule itself is not intended for consumption. Product administration will require the capsules to be opened and the granules to be sprinkled directly in the patients mouth or on a spoon with soft food/yogurt. During a meeting held on February 6, 2019[a] with Diurnal, DMEPA and DMEP conveyed concerns that the design of Alkindi Sprinkle may lead to users swallowing the capsule whole as well as a potential safety issue of choking since this product is intended for pediatric use. Also, it was noted that doses are calculated based on patient BSA and it was unclear to the review team how healthcare professionals would determine an appropriate strength for achieving a calculated dosage that falls within the available capsule strengths. Diurnal was requested to provide a rationale for why a different packaging configuration (b) (4) or dosage form (b) (4) was not chosen and to provide adequate data to support the risk of swallowing the capsule whole is acceptable. In addition, they were also requested to provide mitigation strategies to ensure users understand how to select and administer an appropriate dose.

During a teleconference held on August 22, 2019[b], DMEPA conveyed to the Applicant that DMEPA's evaluation of the June 27, 2019 submission, containing a comprehensive evaluation of the proposed product, use related risk analysis, and human factors validation protocol has identified known use-related risks for similar products (i.e. capsule for non-oral route of administration or capsule that should not be swallowed). We noted that these risks do not represent new or unique risks as compared to other similar products. Therefore, based on the submitted information and postmarket experience with similar products, DMEPA determined that it is not required for the Applicant to submit the results from a human factors (HF) validation study to support their marketing application.

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[a] Johnson, J; Feb 6, 2019 Type C Meeting Minutes; IND 123322; https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804e2775&_afrRedirect=14341064428 34515

[b] Hamilton-Stokes, D; Aug 22, 2019 Meeting Minutes; IND 123322; https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af805106f9&_afrRedirect=14344187325 10460

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Alkindi Sprinkle is provided in a capsule that is not intended to be swallowed. The proposed labeling states that the granules are contained in a capsule carrier which must not be swallowed, but opened carefully. The granules are to be administered directly into the mouth, and should not be chewed, or can be sprinkled onto a spoonful of soft food. We are concerned that this design may lead to administration errors where the capsule may be swallowed whole. This concern was communicated to the Applicant previously (*see Section 1.1, Regulatory History*).

We typically recommend that drug products should not be packaged in a container/closure system that implies or affords a type of administration other than the route or technique intended, unless there are no other options available, because this practice has led to medication errors[c]. For drug products that are granules intended to be sprinkled on food, we recommend packaging into packets (sometimes called sachets) rather than capsules. A capsule

[c] Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors. Food and Drug Administration. 2016. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

can be suggestive of one method of administration (swallowing whole) even though it is not intended, and this would not match the user's expectation of how to use the product.

The Office of Clinical Pharmacology assessed the risk of swallowing the whole capsule and concluded the systemic exposures from administration of intact capsule will likely be similar to when administered as granules and that there does not appear to be a systemic exposure related safety risk upon ingestion of the whole capsule[d]. The review team discussed this concern and determined that the clinical consequence of inadvertently swallowing a capsule is unlikely to have a profound clinical effect.

There is also a risk of choking with the proposed capsule formulation if pediatric patients ingest the entire capsule instead of opening the capsule as recommended. In addition, there is a potential for choking in infants and young children when the granules are poured directly onto the tongue. This concern was discussed with the clinical team in DGE and it has been concluded that the residual risk of choking is considered to be acceptable from a clinical perspective due to the benefit of improved dosing of hydrocortisone in this population. Further, it was conveyed that this risk could be minimized through proper labeling.

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), Medication Guide (MG), container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General			
1.	The proposed formulation and administration instruction may not be appropriate for infants and small children. DMEPA is concerned about the choking hazard in children especially since the medication is specifically to be used in the pediatric population.	Choking hazard in children.	We defer to the clinical team to determine the appropriateness of this formulation and the administration instruction in infants and young children. We recommend consulting the Division of Pediatric and Maternal Health (DPMH) for the appropriateness of administering Alkindi Sprinkle to infants and young children.

[d] Absar, M. Clinical Pharmacology Review for Alkindi Sprinkle (NDA 213876). Silver Spring (MD): FDA, CDER, OCP (US); 2020 MAY 22.

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			Age appropriate administration instruction should be provided in the PI and MG.
2.	Established name and Dosage form displayed inconsistently throughout the label and labeling.	Avoid confusion.	We defer to OPQ to determine the establish name and dosage form for this product. Ensure that the OPQ determined establish name and the dosage form are used throughout the label and labeling.
Prescribing Information –Highlights			
1.	Dosage and Administration section requires revisions.	Improve proper product administration to minimize wrong administration technique errors.	(b) (4)
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2.1- Recommended Dosage Instructions Weight based dosing could result in a dose not commercially proposed.	Prevent wrong dose errors.	Alkindi Sprinkle doses are calculated based on patient BSA. It is unclear how healthcare professionals would determine an appropriate strength for achieving a calculated dosage that falls within the available capsule strengths. DMEPA would recommend providing such guidance in section 2.1 for healthcare professionals.
2.	Section 2.2- Administration Instructions	Improve proper product administration to minimize wrong administration technique errors.	(b) (4)

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	Product administration directions require revisions.		(b) (4)
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
3.	Information on product description is missing, such as imprinting, color and shape.	Improve product identification.	Update this section to include product description of capsule and granules (imprinting, color and shape).
Full Prescribing Information – Section 17 Patient Counseling Information			
1.	Product administration directions require revisions.	Improve proper product administration.	(b) (4)
Medication Guide			
(b) (4)			

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
(b) (4)			

Table 3. Identified Issues and Recommendations for Diurnal (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
ALL Carton Labeling and Container Labels			
1.	Expiration date is undefined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day.

Table 3. Identified Issues and Recommendations for Diurnal (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	Strength presentation is duplicated and competes with net quantity statement.	Improve readability of important information and avoid clutter.	(b) (4)
3.	Route of administration requires revisions.	Improve proper product administration.	
4.	Usual dosage statement requires revisions.	Per 21 CFR 201.55.	

Table 3. Identified Issues and Recommendations for Diurnal (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			(b) (4)
5.	The product identifier required under the drug supply chair security act (DSCSA) is missing.	DSCSA requires manufacturers and repackages, respectively, to affix or imprint a product identifier to each package and homogeneous case of a product intended to be introduced in a transaction in (to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
6.	Format for after open expiration date needs revisions.	Clearly defining the expiration date after product opening will minimize confusion and risk for deteriorated drug medication errors.	Revise the use after open statement to read: "Date of first opening __/__/__. Discard unused portion 60 days after first opening." In addition, this statement should be in bold font. The "__/__/__" statement will alert the users to write a complete date (month, day, and year) on the container label and carton labeling.
Carton Labeling			
1.	Manufacturer statement competes with net quantity statement.	Contributes to clutter of information and delete redundancy.	Consider removing the manufacturer statement on the principle display panel. We note this information is already located on the side panel labeling.

4 CONCLUSION

Our evaluation of the proposed Alkindi Sprinkle Prescribing Information (PI), Medication Guide (MG) container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in **Error! Reference source not found.**Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Diurnal so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Alkindi Sprinkle received on November 29, 2019 from Diurnal, and the listed drug (LD).

Table 2. Relevant Product Information for Alkindi Sprinkle and the Listed Drug

Product Name	**Alkindi Sprinkle**	**Cortef**[e]
Initial Approval Date	N/A	1952
Active Ingredient	hydrocortisone	hydrocortisone
Indication	Replacement therapy in adrenal insufficiency (AI) in infants, children and adolescents (from birth to <17 years)	Treatment in patients with endocrine, rheumatic, ophthalmic, gastrointestinal, respiratory, hematologic, neoplastic, dermatologic and collagen disease and edematous and allergic states.
Route of Administration	oral; capsules containing granules to be opened and administered directly in patients' mouth. The granules must be given orally and should not be chewed. The capsule shell must not be swallowed, but carefully opened and the content administered. The granules are either poured directly onto the child's tongue, or the granules are poured onto a spoon and placed in the child's mouth. For children who are able to take soft food, the granules may be sprinkled onto a spoonful of cold or room temperature soft food (such as yogurt or fruit puree) and given immediately	oral
Dosage Form	Oral granules	Tablet
Strength	0.5 mg, 1 mg, 2 mg and 5 mg	5 mg, 10 mg and 20 mg

[e] Cortef [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 Apr 30. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/008697s036lbl.pdf.

Dose and Frequency	Dose is individualized according to response of patient and is typically between 8 mg/m^2/day to 15 mg/m^2/day given in 3-4 divided doses	Initial dose ranges from 20 mg to 240 mg. Dose is individualized and variable according to disease state and patient response.
How Supplied	50 count capsules in bottle	100 count tablets in bottle
Storage	Stored in original bottle not above 30℃/86°F. Protect from light	Controlled room temperature 20℃ to 25℃ (68F to 77 F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 5, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Alkindi, IND 123322 and NDA 213876. Our search identified previous DMEPA recommendations that were applicable to this review (see section 1.1 above) and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Alkindi Sprinkle labels and labeling submitted by Diurnal.

- Container labels and carton labeling received on May 28, 2019
- Prescribing Information (Image not shown) received on March 11, 2019, available from \\CDSESUB1\evsprod\NDA213876\0004\m1\us
- Medication Guide received on November 29, 2019, available from \\CDSESUB1\evsprod\NDA213876\0001\m1\us

F.2 Label and Labeling Images

Container Labels

(b) (4)

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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MELINA N FANARI
07/15/2020 10:26:44 AM

SEVAN H KOLEJIAN
07/15/2020 11:59:47 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	June 29, 2020
Reviewer:	Amy Chen, PharmD, Safety Evaluator Division of Pharmacovigilance I (DPV-I)
Team Leader:	Christian Cao, MPAS, PA-C DPV-I
Division Director:	Cindy Kortepeter, PharmD DPV-I
Product Name:	Cortef® (hydrocortisone) tablet Alkindi® Sprinkle (hydrocortisone) granules for oral administration
Subject:	Pediatric adverse events
Application Type/Number:	NDA 008697 (Cortef) NDA 213876 (Alkindi)
Applicant/Sponsor:	Pharmacia and Upjohn (Cortef) Diurnal Limited (Alkindi)
OSE RCM #:	2020-978

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of this Pharmacovigilance (PV) Review is to provide the Division of General Endocrinology (DGE) a safety summary and analysis of FDA Adverse Event Reporting System (FAERS) reports for hydrocortisone in pediatric patients less than 18 years old with a diagnosis of adrenal insufficiency (AI) or congenital adrenal hyperplasia (CAH). The primary goal of this safety summary and analysis is to identify potential safety concerns to inform the review of New Drug Application (NDA) 213876 for Alkindi® Sprinkle (hydrocortisone) granules for oral administration indicated for replacement therapy of AI (including AI in CAH) in infants, children and adolescents (from birth to <17 years old).[1]

1.1 BACKGROUND

Alkindi® Sprinkle is a new pediatric-specific presentation of the established active pharmaceutical ingredient hydrocortisone. This same presentation is marketed in the European Union (EU) under the accepted invented name Alkindi[2] and is used interchangeably with Infacort throughout this document. This formulation of hydrocortisone is intended for use in infants, children and adolescents (from birth to <17 years old) as replacement therapy of AI.[2] The NDA 213876 for Infacort is being submitted as a 505(b)(2) application based on the FDA's previous finding of safety and effectiveness for the reference listed drug (RLD) Cortef (NDA 008697).[3] Although hydrocortisone is accepted as appropriate replacement therapy in AI, the availability of current oral products only as solid tablets limits its utility in the pediatric population.[3] The currently available dose strengths do not meet the needs of smaller doses that are required by children up to the age of 17 years.

Adrenal insufficiency is defined by the impaired synthesis and release of adrenocortical hormones.[4] It is classified based upon the mechanism. Primary AI results from disease intrinsic to the adrenal cortex. These patients may present with glucocorticoid deficiency, with or without deficiencies of mineralocorticoids, and adrenal androgens. Central AI is caused by impaired production of adrenocorticotropic hormone (ACTH), secondary pituitary disease that impairs release of ACTH or by interference with corticotropin-releasing hormone (CRH) production from the hypothalamus. Clinical findings associated with glucocorticoid (e.g., cortisol) deficiency include fatigue, nausea, hypoglycemia, increased insulin sensitivity, muscle weakness, and morning headache. As a consequence of cortisol deficiency, there is increased production of pro-opiomelanocortin, which is a prohormone that is cleaved into equimolar amounts of ACTH, melanocyte-stimulating hormone (MSH), and others. The elevated MSH results in increased melanin synthesis, causing hyperpigmentation. This is conspicuous in areas exposed to sunlight or pressure (e.g., elbows and knees) and also in areas not typically exposed to sun, such as palmar creases, axillae, tongue, palate, gingival borders, and scars.

Primary AI is indicated by high ACTH and low cortisol concentrations.[5] In addition to glucocorticoid deficiency, these patients are at risk for mineralocorticoid deficiency, which is indicated by low levels of aldosterone, elevated plasma renin activity (PRA), as well as hyponatremia and or hyperkalemia. Central AI is indicated by low ACTH levels. These patients have glucocorticoid deficiency but not mineralocorticoid deficiency, so PRA and electrolytes are usually normal.

More than 95 percent of cases of CAH are caused by autosomal recessive deficiency of 21-hydroxylase, due to mutations of the CYP21A2 gene.[6] Deficiency of 21-hydroxylase interferes with conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and conversion of progesterone to deoxycorticosterone, resulting in diminished production of cortisol and aldosterone and overproduction of adrenal androgens. The clinical spectrum of disease ranges from severe to mild, depending on the degree of 21-hydroxylase deficiency.[7] Three clinical phenotypes have been described: classic salt-losing, classic non-salt-losing (simple virilizing), and nonclassic (late onset). Females with the classic form (salt-losing and non-salt-losing) present with genital atypia. Males with the salt-losing form who are not identified by neonatal screening present with failure to thrive, dehydration, hyponatremia, and hyperkalemia at 7 to 14 days of life. Males with the classic non-salt-losing form who are not identified by neonatal screening present at two to four years with early virilization (pubic hair, growth spurt, adult body odor). Nonclassic (late onset) may present as early pubarche or sexual precocity in school-age children, hirsutism and menstrual irregularity in young women, or there may be no symptoms. Neonates are usually diagnosed shortly after birth through either an adrenal crisis or the recognition of ambiguous genitalia in females, or in some cases through biochemical screening which is performed in some countries and many USA states during the first week of life.[8]

Six clinical studies have been conducted using Alkindi Sprinkle, specifically four Phase 1 bioavailability and bioequivalence studies in dexamethasone-suppressed healthy adult subjects (studies Infacort 001, 002, 006 and 007) and two Phase 3 efficacy and safety studies in pediatric AI patients (studies Infacort 003 and 004).[1] The overall study population consisted of 100 healthy adult subjects in Phase 1 studies; and 24 pediatric AI patients in study Infacort 003, of whom 18 enrolled in the long-term follow-up study Infacort 004. Infacort 003 was an open-label study in neonates, infants and children less than 6 years of age with adrenal insufficiency.[2] Infacort 004 was an extension study for patients who completed Study Infacort 003 and wished to continue receiving Infacort.[2]

The proposed indication for Alkindi® Sprinkle is replacement therapy of AI (including AI in CAH) in infants, children and adolescents from birth to <17 years old. Alkindi Sprinkle is available as granules contained in capsules for opening in strengths of 0.5 mg, 1 mg, 2 mg and 5 mg. Cortef (hydrocortisone) tablets are approved to treat a wide variety of diseases and disorders including primary or secondary AI and CAH; see Cortef label in Appendix A for all approved indications. Cortef tablets are available in strengths of 5 mg, 10 mg, and 20 mg.

Given the paucity of data in the pediatric population, including the lack of information in pediatric AI patients older than 7 years of age, DGE consulted DPV-I to evaluate FAERS reports for hydrocortisone in pediatric patients less than 18 years old with a diagnosis of AI or CAH to support the review of NDA 213876 for Alkindi® Sprinkle. DGE requested an evaluation of hydrocortisone subdivided by age (0 to <2, 2 to <6, 6 to <12, and 12 to <18 years).

2 PRODUCT LABELS

Given that Infacort is a pediatric formulation of an established product, hydrocortisone, the biopharmaceutic evaluations conducted by Diurnal focused on the bioequivalence between Infacort and immediate-release hydrocortisone, primarily against the reference product Cortef

(Study Infacort 007) as well as a European Union (EU) generic hydrocortisone (Studies Infacort 001 and Infacort 002).[3] The results of the clinical development program for Infacort demonstrated that Infacort is bioequivalent to Cortef and other generic immediate-release hydrocortisone tablets.[3] Accordingly, the product label for Cortef will serve as the RLD to assess for potential safety concerns associated with Alkindi Sprinkle in this review.

The proposed United States Product Insert (USPI) for Alkindi® Sprinke (hydrocortisone) granules for oral administration and current USPI for Cortef® (hydrocortisone) tablet are found in Appendix A.

3 METHODS

3.1 FAERS

DPV-I searched the FAERS database with the strategy described in **Table 1** below.

Table 1. FAERS Search Strategies*

Search Field	All Adverse Events Search	Designated Medical Events (DMEs) Search
Date of search	May 8, 2020	June 13, 2020
Time period of search	Through May 7, 2020	Through June 12, 2020
Search type	FBIS Product Manufacturer Reporting Summary	
Product terms	Product Active Ingredient (PAI): hydrocortisone; hydrocortisone aceponate; hydrocortisone acetate; hydrocortisone butyrate; hydrocortisone cypionate; hydrocortisone hemisuccinate; hydrocortisone hemisuccinate anhydrous; hydrocortisone phosphate; hydrocortisone probutate; hydrocortisone sodium phosphate; hydrocortisone sodium succinate; hydrocortisone valerate; hydrocortisone\hydrocortisone acetate; hydrocortisone\hydrocortisone acetate\hydrocortisone butyrate\hydrocortisone sodium phosphate\hydrocortisone sodium succinate\hydrocortisone valerate; hydrocortisone\hydrocortisone acetate\hydrocortisone cypionate\hydrocortisone sodium succinate; hydrocortisone\hydrocortisone acetate\hydrocortisone sodium succinate	
MedDRA terms (version 23.0)	All	Event list: DME† list

* See Appendix B for a description of the FAERS database.
† See Appendix C for a list of the Office of Surveillance and Epidemiology's (OSE) DMEs

4 RESULTS

4.1 FAERS

The FAERS search described in **Table 1** for all adverse events for hydrocortisone[a] yielded 13,106 reports. After filtering by ages 0 to <18 years and listed reason for use as AI or CAH, 74 reports of hydrocortisone in pediatric patients less than 18 years old with a diagnosis of AI or CAH were identified.

[a] Hydrocortisone includes reports of Cortef as well as other formulations of hydrocortisone including generics.

For the purposes of this PV review a case-level analysis was not performed on all reports; case-level review was conducted for select adverse events of interest identified from analysis of the high-level FAERS data. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes; causality and the role of the product in the coded outcome have not been determined for all reports (see Appendix A for FAERS limitations).

Table 2 provides the descriptive characteristics of the 74 FAERS reports of pediatric patients (ages 0 to <18 years) who used hydrocortisone for AI or CAH retrieved by the search strategy described in **Table 1** and subsequent filtering described above.

Table 2. Descriptive Characteristics of FAERS Reports with Hydrocortisone used for Adrenal Insufficiency or Congenital Adrenal Hyperplasia, in Pediatric Patients (Ages 0 to <18 Years) Received by FDA Through May 7, 2020

n=74

Characteristic		Result
Sex	Male	34
	Female	39
	Unknown	1
Age	0 to <2 years	16
	2 to <6 years	7
	6 to <12 years	19
	12 to <18 years	32
Country	United States	46
	Foreign*	28
Report type	Expedited	49
	Direct	10
	Periodic	15
Serious outcomes†	Death	5
(n=64)	Life-threatening	5
	Hospitalization	27
	Disability	3
	Other serious	37

* Foreign countries included Japan (7), Germany (4), Australia (3), India (3), Italy (3), France (2), Great Britain (2), Hungary (1), Korea (1), China (1), and Morocco (1).

† For the purposes of this document the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, or other serious important medical events. A report can have one or more serious outcome.

Table 3 lists the reported MedDRA Preferred Terms (PTs) in order of frequency in the 74 FAERS reports and the labeling status of each PT per the Cortef and proposed Alkindi Sprinkle labels.

Table 3. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 2 with Hydrocortisone used for Adrenal Insufficiency or Congenital Adrenal Hyperplasia in Pediatric Patients (Ages 0 to <18 Years) Received by FDA Through May 7, 2020 Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of FAERS Reports*	Labeled (Yes/No), Location† or Other Category (Cortef)	Labeled (Yes/No), Location† or Other Category (Alkindi Sprinkle)
Adrenocortical insufficiency acute	12	No, DR‡	Yes, IR
Drug interaction	7	No	No
Adrenal insufficiency	5	No, DR§	Yes, IR
Cushingoid	5	Yes, AR (Cushingoid state)	Yes, WP (Cushing syndrome)
Drug ineffective	5	No, U	No
Hypoglycaemia	5	Yes, AR (Manifestation of latent diabetes mellitus)	No
Malaise	5	No, DR	No
Alcohol interaction	4	No	No
Condition aggravated	4	No, U	No
Hypotension	4	No, DR	No
Product quality issue	4	No, U	No
Vomiting	4	No, DR	No
Fatigue	3	No, DR	No
Growth retardation	3	Yes, AR (Suppression of growth)	Yes, WP, MG
Hyperkalaemia	3	No, DR	No
Hyponatraemia	3	No, DR	No
Medication error	3	No	No
Product substitution issue	3	No, U	No
Short stature	3	Yes, AR (Suppression of growth)	Yes, WP, MG (Growth retardation)
Acidosis	2	No, DR	No
Adrenal atrophy	2	No, DR	No
Adrenogenital syndrome	2	No, DR‖	Yes, IR
Anaphylactic reaction	2	No	No
Anxiety	2	Yes, P (Emotional instability)	Yes, MG (Anxious)
Asthenia	2	No, DR	No
Blood corticotrophin abnormal	2	No, DR	No
Blood corticotrophin increased	2	No, DR	No
Cardio-respiratory arrest	2	No, DR	No
Cataract	2	Yes, W, AR (Posterior subcapsular cataracts)	Yes, WP
Device related sepsis	2	Yes, W, P (Infections)	Yes, WP (Infections)
Diabetes mellitus	2	Yes, AR (Manifestations of latent diabetes mellitus)	No
Headache	2	Yes, AR	No
Hypokalaemia	2	Yes, W (Increased excretion of potassium) AR (Potassium loss)	Yes, AR, MG (Hypokalemic alkalosis)

Table 3. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 2 with Hydrocortisone used for Adrenal Insufficiency or Congenital Adrenal Hyperplasia in Pediatric Patients (Ages 0 to <18 Years) Received by FDA Through May 7, 2020 Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of FAERS Reports*	Labeled (Yes/No), Location† or Other Category (Cortef)	Labeled (Yes/No), Location† or Other Category (Alkindi Sprinkle)
Incorrect route of product administration	2	No	No
Insomnia	2	Yes, P	No
Lethargy	2	No, DR	No
Off label use	2	No ¶	No
Osteoporosis	2	Yes, P, AR	Yes, W, AR, MG (Reduced bone mineral density)
Pleural effusion	2	No, DR	No
Pneumatosis	2	No	No
Product dispensing error	2	No	No
Pulmonary congestion	2	No, DR	No
Reaction to excipient	2	No, U	No
Staphylococcal infection	2	Yes, W, P (Infections)	Yes, WP (Infections)
Streptococcal infection	2	Yes, W, P (Infections)	Yes, WP (Infections)
Ureterolithiasis	2	No, DR	No

* A report can contain more than one MedDRA PT.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.
‡ *Adrenocortical insufficiency acute* (PT) is also indication related.
§ *Adrenal insufficiency* (PT) is also indication related.
‖ *Adrenogenital syndrome* (PT) is also indication related.
¶ *Off label use* (PT) are of miscoded reports
Abbreviations: C= Contraindications, W = Warnings, P = Precautions, AR = Adverse Reactions, = MG= Medication Guide, DR = Disease-related, U = Uninformative

Adverse events related to endocrine and metabolism disorders in **Table 3** were the most commonly reported PTs (45) and included *Adrenocortical insufficiency acute* (12), *Adrenal insufficiency* (5), *Cushingoid* (5), *Hypoglycaemia* (5), *Hyperkalaemia* (3), *Hyponatraemia* (3), *Acidosis* (2), *Adrenal atrophy* (2), *Blood corticotrophin abnormal* (2), *Blood corticotrophin increased* (2), *Diabetes mellitus* (2), and *Hypokalaemia* (2). Adverse events related to general system disorders not elsewhere classified were the second most commonly reported category of PTs (16) and included *Malaise* (5), *Condition aggravated* (4), *Fatigue* (3), *Asthenia* (2), and *Lethargy* (2). Generally, these AEs are likely related to ongoing adrenal insufficiency, underdosing, excess dosing of hydrocortisone, or normal pediatric illnesses seen with the use of any chronic medication.

Reports with the following unlabeled PTs identified from **Table 3** and from Appendix E (list of PTs with n=1) were determined as confounded by concomitant disease or concomitant drug: *Alcohol interaction, Hypotension, Cardio-respiratory arrest, Pleural effusion, Pulmonary congestion, Ureterolithiasis*, *Blood bilirubin increased, Cardiac death, Lymphocyte count decreased, Myelodysplastic syndrome unclassifiable, Neutrophil count decreased, Platelet count decreased, Septic shock,* and *White blood cell count decreased*. For example, the reports coded with the PT *Alcohol interaction,* which represents one report with three duplicates, describes a 17-year old female patient with a history of diabetes who developed hypoglycemia after drinking

alcohol while on therapy with hydrocortisone for Addison's disease. The event was confounded by concomitant use of insulin.

Although only PTs with a frequency ≥ 2 are listed in **Table 3**, we reviewed all PTs for new potential safety signals. Review of reports with a PT with a frequency of n=1 in Appendix D identified one additional PT of interest: *Left ventricular hypertrophy*. Left ventricular hypertrophy is not listed in the label for Cortef and will be discussed further below.

4.1.1 Analysis of Fatal Reports

Of the 74 FAERS reports for hydrocortisone, five reported a fatal outcome. The causes of death in three reports were cardiorespiratory arrest (1), cardiac death due to hyperkalemia (1), and septic shock (1). The fourth report described a 16-year old male patient who received gemtuzumab as part of an expanded access protocol for the treatment of acute myelogenous leukemia in patients who may benefit from treatment and have no access to alternative therapy. When treatment became palliative, several medications were discontinued including gemtuzumab, methylprednisolone, and hydrocortisone. No autopsy was performed; however, the physician reported the patient died due to stridor. The remaining report was a duplicate of the gemtuzumab report.

4.1.2 Analysis by Designated Medical Events

Designated Medical Events (DMEs) are adverse events that are considered serious and, from a pharmacovigilance perspective, may often be caused by exposure to drugs from many pharmacological or therapeutic classes. Identification of these events is a priority, even when the number of cases is small, and before there is evidence of disproportional reporting. DMEs are not intended to include events with a high prevalence in the general population. See Appendix C for a list of the Office of Surveillance and Epidemiology's (OSE) DMEs.

The FAERS search for DMEs described in **Table 1** yielded 1,274 reports.

After filtering by ages 0 to <18 years and listed reason for use as AI or CAH, three reports in pediatric patients less than 18 years old with a diagnosis of AI or CAH were identified with the PTs *Anaphylactic reaction* (n=2) and *Seizure* (n=1). One report (FAERS # 3199599) described a 7-year old male with an underlying history of seizure disorder who developed seizures while receiving a specific lot Cortef (hydrocortisone cypionate) to treat AI, which resolved after switching to another lot. Seizure is listed in the Cortef oral suspension label as "Convulsions" under the Adverse Reactions section. (b) (4) . Anaphylactic reaction is not listed in the Cortef (b) (4) . The two reports (FAERS # 7441742 and 6418609) with the PT *Anaphylactic reaction* are duplicates of each other and described an 11-year-old male patient who developed an anaphylactic reaction described as swollen lips and face, tightness in his throat, sneezing, rhinorrhea, generalized hives, cough, and difficulty breathing 1 or 2 minutes after receiving Solu-Cortef (hydrocortisone sodium succinate) intramuscularly to treat Addison's disease. Concomitant medications included oral hydrocortisone and fludrocortisone. The patient was skin tested with Solu-Cortef and found to be positive. He was treated in the emergency room but the treatment and outcome were unknown. Solu-Cortef is labeled for anaphylaxis in the Adverse Reactions section.[9]

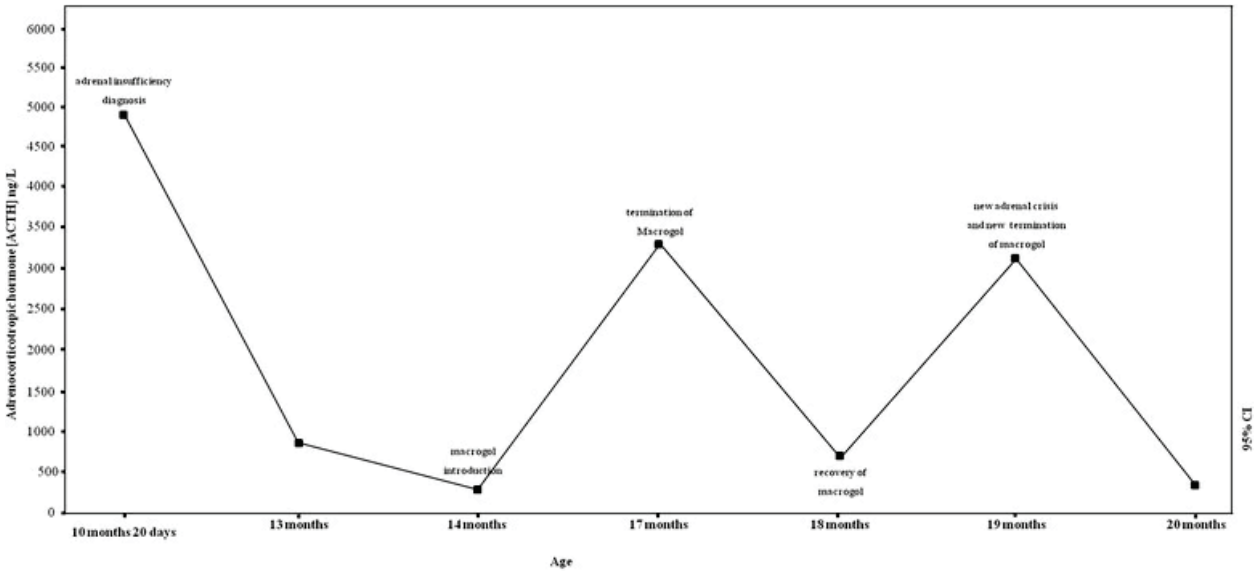
4.1.3 Analysis by Pediatric Age Groups

An analysis of reports of notable PTs by the pediatric age groups 0 to <2 and 12 to <18 years is provided as follows. No notable PTs were identified for the age groups 2 to <6 and 6 to <12.

Age 0 to <2 Years:

- ***Drug interaction – with polyethylene glycol (2):*** One report, with one duplicate, that was also published in the medical literature reported malabsorption of hydrocortisone secondary to polyethylene glycol (PEG) use for constipation in a girl with congenital adrenal insufficiency.[10] An 11-month old female patient taking glucocorticoid (hydrocortisone 15 mg/m^2/day) and "fluorocortisone 0.2 mg/day" for adrenal deficiency started PEG twice daily for constipation. The PEG was typically taken 30 to 60 minutes after taking the hydrocortisone and fluorocortisone. After 3 months of PEG therapy, routine follow-up tests revealed sodium was 135 mEq/L, potassium 5.3 mEq/L, renin 124.2 µU/mL, cortisol 1.78 µg/dL, and ACTH 3262 ng/L indicating the insufficient control of the patient's adrenal insufficiency. The PEG was stopped, which resulted in a rapid reduction of ACTH (648 ng/L after 28 days). The patient's family arbitrarily reintroduced PEG once daily; this time, given more than 2 hours after taking hydrocortisone and fluorocortisone. After 1 month, during a respiratory tract infection, the patient presented with hypoglycemia, lethargy, weakness, and hypotonia. Tests revealed that the patient was in adrenal crisis with, glucose 36 mg/dL, sodium 132 mEq/L, potassium 5.4 mEq/L, and ACTH 3145 ng/L. The adrenal deficiency was treated and the PEG stopped with near normalization of corticotropin (323 ng/l) after 23 days. Figure 1 provides a time course of corticotropin serum levels relative to the administration of the PEG.

Figure 1. Corticotropin serum levels during PEG dosing*



* Stagi S, Del Greco P, Ricci F, Iurato C, Poggi G, Seminara S, et al. Hydrocortisone malabsorption due to polyethylene glycols (Macrogol 3350) in a girl with congenital adrenal insufficiency. Italian Journal of Pediatrics 2014;40 (78):01-07

- ***Pneumatosis (2):*** Review of the FAERS data identified one report and one duplicate reporting gastric pneumatosis without evidence of intestinal obstruction following hydrocortisone for treatment of adrenal insufficiency.[11] A premature female infant (24 and 6/7 week's gestation) developed respiratory distress syndrome and hypotension after birth requiring mechanical ventilation with surfactant and a dopamine drip. It was also presumed the patient had an adrenal insufficiency with tests demonstrating a low cortisol level (2.6 µg/dL) and thus, the patient was initiated on hydrocortisone (1 mg/kg every 6 hours). Hydrocortisone was stopped on day 8 but then restarted due to low blood pressures and low repeat random cortisol level (5 µg/dL). At 12 days of age, gastric pneumatosis, portal venous gas, and pneumoperitoneum were incidentally noted on an abdominal radiograph obtained for central line placement. As well, the patient developed progressive abdominal distension. Physical exam was notable for bluish discoloration of her central abdomen and tenderness to palpation. Exploratory laparotomy revealed free air in the abdominal cavity, diffuse gastric pneumatosis, and patchy discoloration of the stomach wall without identifiable perforation. There was no evidence of intestinal obstruction. Hydrocortisone was subsequently discontinued and the patient was treated empirically with broad spectrum antibiotics to limit bacterial translocation and a proton pump inhibitor to treat gastritis. One week post-operatively, a contrast study demonstrated normal gastric anatomy without evidence of perforation, obstruction, strictures, or atresias. Enteral feedings were restarted and the patient recovered uneventfully thereafter.

- ***Left ventricular hypertrophy (1):*** One FAERS report provided information about the development of left ventricular hypertrophy (LVH) in a child treated with hydrocortisone that appeared to be dose-related.[12] The patient, who is a male infant diagnosed with CAH at one month old, initiated therapy with hydrocortisone 10 mg daily and "fluorohydrocortisone" 100 mg daily. At the start of therapy, physical exam and electrocardiogram (ECG) were normal. One month later, following the occurrence of asthenia and severe loss of appetite, the hydrocortisone dosage was increased to 25 mg three times daily with improvement of these symptoms. At 11 months of age, the patient was hospitalized (reason for admission not reported) where he showed a previously absent systolic murmur without signs of heart failure. ECG showed signs of LVH and echocardiography revealed "significant" LVH with outflow tract obstruction and mitral valve incompetence. These findings prompted a reduction in the dosage of hydrocortisone to 10 mg three times daily. At 13 months of age, ventricular arrhythmias were recorded on an Holter ECG. Blood pressure was 100/56 mmHg and an ECG showed the same signs of LV overload and normal QT interval. Propranolol was then started. After one month of therapy, ventricular arrhythmias disappeared from the Holter recording and echocardiography showed a reduction in the midventricular gradient, however, with persistence of ventricular wall thickening. At the age of 3.8 years, hydrocortisone dosage was 10 mg daily and an echocardiography showed a "significant" reduction in wall thickness. At the age of 5.6 years, following normalization of Holter ECG, the propranolol was discontinued. Furthermore, echocardiography showed normal wall thickness and contractility. At the time of the report, the patient was eight years old and was receiving hydrocortisone 10 mg daily and fluorohydrocortisone 100 mg daily with good metabolic control and no cardiac relapse.

Age 12 to <18 Years

- ***Drug interaction – with ethosuximide (2):*** Review of the FAERS data identified one report and one duplicate of a potential drug interaction between ethosuximide and hydrocortisone from a published article.[13] The authors of the article reported a female patient, 12-years-old at time of report, with salt-wasting CAH (diagnosed at birth) who required constant adjustments of her hydrocortisone dosage to maintain sufficient suppression after initiating concomitant therapy with ethosuximide for treatment of absence seizures at age 6.5 years. Prior to ethosuximide therapy, baseline labs showed 17-hydroxyprogesterone (17-OHP) was 1960 ng/dL, androstenendione 48 ng/dL, and testosterone 4.1 ng/dL on standard doses of hydrocortisone (14.5 mg/m^2 per day) and fludrocortisone (0.15 mg/day). At 7.4 years old while on ethosuximide 500 mg daily, serum 17-OHP levels increased to 9250 ng/dL, androstenedione 229 ng/dL, and testosterone 51 ng/dL. The patient subsequently required progressive increases in her hydrocortisone dose, up to 23.5 mg/m^2 per day, to achieve adequate adrenal control. Ethosuximide was gradually escalated to control her seizures with a maximum intake of 1.5 g/day. Each increase in ethosuximide required a concurrent increase in hydrocortisone to a maximum of 28 mg/m^2 per day to maintain adrenal control. At the age of 12.2 years, the patient developed generalized tonic-clonic seizures and therefore, was transitioned to valproate with ethosuximide tapered off over a period of 3 months. The change in anticonvulsant therapy was accompanied by a decrease in glucocorticoid requirements. At 12.3 years old, 17-OHP was 50 ng/dL, androstenedione 17 ng/dL, and testosterone 5 ng/dL, and with hydrocortisone 25 mg/m^2 per day. Repeat assessment at 12.6 years of age was significant for increased body mass index, cushingoid appearance, and suppressed serum androgens; therefore, hydrocortisone was decreased to 16 mg/m^2 per day from 20 mg/m^2 per day at that time. Throughout, fludrocortisone supplementation remained unchanged.

- ***Drug interaction – with rifampin (3):*** Three FAERS reports coded with the PT *Drug interaction,* of which two were duplicates, was of a published article about a drug interaction between rifampin and hydrocortisone leading to adrenal crisis.[14] A 12-year old female was receiving rifampin to treat adrenal gland tuberculosis when she received hydrocortisone and fludrocortisone to treat AI. She subsequently presented to the emergency room (ER) with elevated ACTH levels and was diagnosed with rifampin induced metabolism of steroids leading to corticosteroid insufficiency. The patient started dexamethasone, which was continued for the course of anti-tuberculosis therapy with rifampin. She later restarted hydrocortisone after completing the course of rifampin and remained stable. Drug interaction with rifampin appears under the Precautions section of product labeling for Cortef.

5 REVIEWER COMMENTS

Based on the analysis of FAERS data for hydrocortisone used in pediatric patients for AI or CAH, DPV-I identified four notable adverse events, which are all unexpected and not listed in either the Cortef USPI or in the proposed USPI for Alkindi: 1) malabsorption due to concomitant use of polyethylene glycol, 2) drug interaction with ethosuximide, 3) gastric pneumatosis, and 3) left ventricular hypertrophy. Our analysis did not identify any expected (i.e., labeled) adverse events with apparent increase in severity. We, however, noted several reports of medication

errors and compounding issues. These reports were commonly related to problems with dosing in the pediatric patient, thus supporting the need for smaller available doses of hydrocortisone.

Of the pediatric population <18 years of age, most of the adverse events occurred in the youngest age group (0 to <2 years). No safety issues were identified in patients between 2 to <12 years of age. This finding may indicate that the youngest patients are most susceptible to adverse reactions including infants and neonates due to prematurity and low birth weight associated with underdevelopment.

A discussion of the four unexpected adverse events or safety concern is provided below.

Malabsorption due to polyethylene glycol

The first notable safety concern was identified from the published case report of hydrocortisone malabsorption due to concomitant PEG use in an 11-month-old female infant with CAH triggering an adrenal crisis.[10] The time course of ACTH levels following discontinuation of PEG administration support this hypothesis of PEG causing malabsorption of the oral hydrocortisone (see **Figure 1** on page 10 above). We acknowledge this patient was also concomitantly taking "fluorocortisone" with hydrocortisone and PEG, which may have contributed to the malabsorption of this drug. Given the weak glucocorticoid activity of fluorocortisone relative to its mineralocorticoid activity, it may be inferred that significant changes in ACTH levels were likely due to the malabsorption of hydrocortisone, which has strong glucocorticoid effects. The authors indicated that many physiological gastrointestinal factors may influence the plasma concentration-time profile of hydrocortisone; however, hydrocortisone has a high permeability in both the small and large intestines, and the short elimination half-life (near 1.5 hours) requires two or more dose administrations per day highlighting the potential significance of this potential interaction.[15] By way of action of the PEG to shorten gastrointestinal transit time, it is reasonable to suspect that its use may lead to decreased absorption, if not malabsorption, of the hydrocortisone, and possibly with other orally administered drugs as well.

Review of the FAERS data retrieved for all reports of hydrocortisone regardless of patient's age or reason for use identified 250 reports with the PT *Drug interaction* of which, there were four reports that listed PEG as a co-suspect product. These four reports, however, were all duplicates of the sentinel report summarized above. Search of PubMed did not identify additional case reports or any studies to further support this potential safety signal.

Drug interaction with ethosuximide

The second notable safety concern described a drug interaction between hydrocortisone and ethosuximide in a girl with CAH who required constant hydrocortisone dose adjustments after initiating ethosuximide for treatment of absence seizures.[13] The drug interaction appeared to be due to an inductive effect of ethosuximide on the metabolism of hydrocortisone, which was supported by the elevation of serum adrenal androgen levels following administration of the ethosuximide. It was also noted that each increase in ethosuximide intake required a concurrent or subsequent increase in hydrocortisone dose to maintain adequate adrenal control, further supporting the possibility that ethosuximide induces the clearance of exogenously administered glucocorticoids (e.g., hydrocortisone). When the patient was transitioned from ethosuximide to

valproate upon development of tonic-clonic seizures, the change in anticonvulsant therapy was followed by a decrease in glucocorticoid requirements.

Although ethosuximide is not known to be an inducer of CYP enzymes,[16] hydrocortisone is metabolized by cytochrome P450 3A4 (CYP3A4). Ethosuximide may induce the hepatic clearance of hydrocortisone; although, further investigation is needed to elucidate the mechanism.

No additional reports were identified in FAERS or the medical literature describing a drug-drug interaction between concomitant uses of hydrocortisone and ethosuximide.

Gastric pneumatosis

Gastric pneumatosis was a notable adverse event identified from a report of a low birthweight premature neonate treated with postnatal steroids for relative AI.[11] The latency from initiation of a second course of hydrocortisone to identification of the gastric pneumatosis was four days. The time to onset may have been shorter given the gastric pneumatosis was only incidentally noted on an abdominal radiograph for central line placement. The temporal relationship between the onset of gastric pneumatosis and administration of hydrocortisone suggests an association. The recovery of gastric pneumatosis following hydrocortisone withdrawal is also consistent with a drug-related effect.

It has been hypothesized that acute glucocorticoid administration may elevate levels of the cytokine transforming growth factor beta, which increases Smad2/3 phosphorylation leading to inhibition of cell proliferation and induction of apoptosis in the gastric epithelium.[17] The authors of the case report speculate that this infant's immature gastric mucosal barrier may have been further compromised by steroid administration precipitating intraluminal gas dissection into her stomach wall.[18]

No additional reports of gastric pneumatosis were identified in FAERS or the medical literature.

Left ventricular hypertrophy

The final notable adverse event was of marked LVH in an 11-month old male treated with high dose hydrocortisone therapy for CAH.[12] The high dose hydrocortisone regimen resulted in LVH with outflow tract obstruction, mitral valve incompetence, and arrhythmias, which were absent prior to steroid therapy shown by the ECG and echocardiography at one month of age. The temporal relationship between the onset of cardiac hypertrophy and the administration of hydrocortisone coupled by the reversal of cardiomyopathy upon dose reduction of hydrocortisone supports a causal association between LVH and hydrocortisone. LVH mimicking hypertrophic cardiomyopathy has been related to the hypertensive state induced by steroid therapy; however, the normal blood pressures reported in the patient does not support the theory of a secondary compensatory hypertrophic state. The direct effect of steroids on cardiac myocytes is suggested by studies on neonatal rat myocytes indicating an induction of LVH after exposure to dexamethasone, with increased heart weight to body weight ratio as well as increase of protein content (e.g., actin) in the myocardium.[19] Glucocorticoids also stimulate gluconeogenesis with a secondary hyperglycemic and hyperinsulinemic effect. A combined effect of insulin and corticosteroids has been reported to induce hypertrophic cardiomyopathy in

two infants.[20] The normalization of cardiac morphological changes and clinical signs in this patient after the dose reduction of hydrocortisone, suggests that the effect of hydrocortisone on cardiac muscle are dose-dependent and reversible.

A search in FAERS and the medical literature identified one report in the literature; none from FAERS. The published case report was of a premature female infant who developed hypertrophic cardiomyopathy after receiving hydrocortisone to treat broncho-pulmonary dysplasia.[21] This female infant was delivered at 23 weeks gestation (birth weight 640 g) by Caesarean section in a 34-year-old multigravida mother with a history of recurrent fetal loss. After resuscitation, she was ventilated and put on inotropic support in view of acidosis and shock. Surfactant was administered on the first day of life. The patient was given intravenous hydrocortisone from the third day of life for the treatment of respiratory distress syndrome. On day 8, the patient was noted to have a harsh murmur. Echocardiography revealed concentric hypertrophy of the right and left ventricles with a peak gradient of 50 mm Hg across the left ventricular outflow tract (LVOT) and left ventricular fractional shortening of 35%. Steroids were discontinued after 5 days and the patient was extubated on day 17. Echocardiography done after three weeks showed resolution of left ventricular hypertrophy. The patient had to be reintubated on day 33 for respiratory distress and hydrocortisone was restarted for the management of chronic lung disease. Echocardiography a week after restarting hydrocortisone showed hypertrophy of both ventricles with "significant" dynamic LVOT obstruction but with good ventricular function. Steroids were eventually discontinued. The patient was extubated on day 41 and discharged at 3 months of age. Serial echocardiography showed gradual resolution of the LVH. The temporal relationship between the administration of hydrocortisone and the onset of hypertrophic cardiomyopathy suggests a drug related effect. Recurrence of the event on re-initiating steroids and resolution upon discontinuation of the drug further supports an association between hydrocortisone and hypertrophic cardiomyopathy.

6 CONCLUSION

Overall, the adverse events identified in this postmarketing review of pediatric FAERS reports for hydrocortisone used to treat AI or CAH were generally consistent with the labeling for Cortef tablets and proposed labeling for Alkindi Sprinkle. DPV-I identified four safety concerns including malabsorption of hydrocortisone due to concomitant PEG use, drug interaction with ethosuximide, gastric pneumatosis, and left ventricular hypertrophy that may inform the review for Alkindi Sprinkle (NDA 213876).

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. PROPOSED ALKINDI SPRINKLE AND CORTEF USPI


Alkindi Sprinkle label.pdf


Cortef label.pdf

8.2 APPENDIX B. DATABASE DESCRIPTION

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. LIST OF OSE DESIGNATED MEDICAL EVENTS

System Organ Class	Preferred Terms (MedDRA 23.0)
Blood and lymphatic system disorders	Agranulocytosis
	Aplastic anaemia
	Bone marrow failure
	Coombs negative haemolytic anaemia
	Coombs positive haemolytic anaemia
	Haemolytic anaemia
	Pancytopenia
	Thrombotic thrombocytopenic purpura
Cardiac Disorders	Torsade de pointes
	Ventricular fibrillation
Ear and labyrinth disorders	Deafness
	Deafness bilateral
	Deafness neurosensory
	Deafness permanent
	Deafness transitory
	Deafness unilateral
	Ototoxicity
	Sudden hearing loss
Eye Disorders	Blindness
	Blindness transient
	Blindness unilateral
	Optic ischaemic neuropathy
	Sudden visual loss
	Toxic optic neuropathy
Gastrointestinal Disorders	Haemorrhagic necrotic pancreatitis
	Pancreatic necrosis
	Pancreatitis haemorrhagic
	Pancreatitis necrotising
General disorders and administration site conditions	Sudden cardiac death
	Sudden death
Hepatobiliary Disorders	Acute hepatic failure
	Drug-induced liver injury
	Hepatic failure
	Hepatic necrosis
	Hepatitis fulminant
Immune System Disorders	Anaphylactic reaction
	Anaphylactic shock
	Anaphylactoid reaction
	Anaphylactoid shock

System Organ Class	Preferred Terms (MedDRA 23.0)
Infections and Infestations	Progressive multifocal leukoencephalopathy
	Suspected transmission of an infectious agent via product
	Transmission of an infectious agent via product
Investigations	Electrocardiogram QT prolonged
Musculoskeletal and connective tissue disorders	Myopathy toxic
	Rhabdomyolysis
Nervous system disorders	Generalised tonic-clonic seizure
	Seizure
	Serotonin syndrome
	Status epilepticus
Product Issues	Product compounding quality issue
	Product contamination
	Product contamination chemical
	Product contamination microbial
	Product contamination physical
Psychiatric Disorders	Completed suicide
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis
	Drug reaction with eosinophilia and systemic symptoms
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Surgical and Medical Procedures	Liver transplant

8.4 APPENDIX D. PREFERRED TERMS WITH N=1 WITH HYDROCORTISONE USED FOR ADRENAL INSUFFICIENCY OR CONGENITAL ADRENAL HYPERPLASIA IN PEDIATRIC PATIENTS (AGES 0 TO <18 YEARS) THROUGH MAY 7, 2020

17-hydroxyprogesterone decreased; Abdominal discomfort; Abdominal distension; Abdominal pain; Abnormal behaviour; Addison's disease; Adverse drug reaction; Agitation; Arthralgia; Blood androstenedione decreased; Blood bilirubin increased; Blood glucose decreased; Blood glucose increased; Blood pressure abnormal; Blood sodium decreased; Blood testosterone decreased; Bone tuberculosis; Cardiac death; Cardiac failure; Cardiac failure congestive; Cardiomyopathy; Coeliac disease; Cortisol decreased; Crying; Cushing's syndrome; Dehydration; Depression; Diabetic ketoacidosis; Disease recurrence; Drug dependence; Drug level below therapeutic; Drug screen negative; Dysgeusia; Dyspnoea; Educational problem; Encephalopathy; Eye swelling; Feeling abnormal; Fluid retention; Gastroenteritis; Gastrooesophageal reflux disease; Glycosylated haemoglobin increased; Graft versus host disease; Hydronephrosis; Hydroureter; Hypercalcaemia; Hypercalciuria; Hypersensitivity; Hypertriglyceridaemia; Hypocalcaemia; Hypotonia; Influenza; Intentional product use issue; Intercepted medication error; Intracranial pressure increased; Irritability; Ischaemic stroke; Laboratory test abnormal; Left ventricular hypertrophy; Loss of consciousness; Loss of personal independence in daily activities; Lymphadenopathy; Lymphocyte count decreased; Mobility decreased; Myelodysplastic syndrome unclassifiable; Nasopharyngitis; Nausea; Nervousness; Neutrophil count decreased; Pain; Pancreatitis acute; Platelet count decreased; Pneumatosis intestinalis; Polyuria; Post transplant lymphoproliferative disorder; Product formulation issue; Product odour abnormal; Product preparation error; Product taste abnormal; Product use in unapproved indication; Pruritus; Psychomotor hyperactivity; Pulmonary oedema; Pyrexia; Quality of life decreased; Rebound effect; Renin abnormal; Renin increased; Respiratory distress; Screaming; Seizure; Self esteem decreased; Sepsis; Septic shock; Sneezing; Social avoidant behaviour; Surgery; Tachycardia; Therapeutic product effect decreased; Therapy change; Treatment noncompliance; Viral infection; Von hippel-lindau disease; Weaning failure; Weight decreased; Weight increased; White blood cell count decreased; Wrong technique in product usage process

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