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

Pediatric Postmarketing Pharmacovigilance Review

Date:	February 22, 2024
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Product Name:	Cafcit injection (caffeine citrate injection, USP)
Pediatric Labeling Approval Date:	March 2, 2020
Application Type/Number:	NDA 020793
Applicant:	Hikma Pharmaceuticals USA, Inc.
TTT Record ID:	2023-7534

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cafcit injection (caffeine citrate injection, USP) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with caffeine citrate injection in pediatric patients.

Cafcit injection (caffeine citrate injection, USP) is a central nervous system stimulant that was initially approved in the U.S. on September 21,1999. Cafcit injection is currently indicated for the treatment of apnea of prematurity.

In accordance with BPCA, section 409i of the Public Health Service Act, and in consultation with stakeholders including FDA, the National Institute for Child Health and Human Development (NICHD) added caffeine citrate to the BPCA priority list of therapeutics in critical need of further study in pediatric populations. Under contract to NICHD, the Duke Clinical Research Institute (DCRI) developed Pediatric Trials Network (PTN) protocol NICHD-2014-CAF01 titled "Safety and efficacy of caffeine citrate in premature infants." To evaluate safety in premature infants receiving caffeine citrate, NICHD-2014-CAF01 utilized data from a retrospective analysis of clinical data for premature infants treated with caffeine per standard of care together with an analysis of aggregate data published from the randomized, controlled Caffeine for Apnea of Prematurity Trial (NCT00182312). FDA reviewed findings from NICHD-2014-CAF01 and the requested labeling changes for Cafcit injection.

On March 2, 2020, FDA approved labeling changes for Cafcit injection that:

- Expanded the indication to include use in premature infants of a broader gestational age
- Allowed for longer treatment duration
- Included more details from a published randomized, placebo-controlled, clinical trial that studied the use of caffeine citrate in apnea of prematurity in approximately 2000 patients and found that necrotizing enterocolitis was not more common in patients treated with caffeine compared with patients treated with placebo
- Included updates to the DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS section of the product labeling

This review was prompted by the March 2, 2020, pediatric labeling changes. DPV has not previously performed a pediatric postmarketing pharmacovigilance review for Cafcit injection for the Pediatric Advisory Committee.

DPV searched FAERS for all reports with caffeine citrate injection in pediatric patients less than 17 years of age from September 21, 1999 – December 11, 2023, and identified 43 reports. However, all 43 reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths that could be attributed to caffeine citrate injection in pediatric patients less than 17 years of age.

DPV did not identify any new pediatric safety concerns for caffeine citrate injection at this time and will continue routine pharmacovigilance monitoring for caffeine citrate injection.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cafcit injection (caffeine citrate injection, USP) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with caffeine citrate injection in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Cafcit injection (caffeine citrate injection, USP) is a central nervous system stimulant that was initially approved in the U.S. on September 21, 1999. Cafcit injection is currently indicated for the treatment of apnea of prematurity.[1]

In accordance with BPCA, section 409i of the Public Health Service Act, and in consultation with stakeholders including FDA, the National Institute for Child Health and Human Development (NICHD) added caffeine citrate to the BPCA priority list of therapeutics in critical need of further study in pediatric populations. Under contract to NICHD, the Duke Clinical Research Institute (DCRI) developed Pediatric Trials Network (PTN) protocol NICHD-2014-CAF01 titled "Safety and efficacy of caffeine citrate in premature infants." To evaluate safety in premature infants receiving caffeine citrate, NICHD-2014-CAF01 utilized data from a retrospective analysis of clinical data for premature infants treated with caffeine per standard of care together with an analysis of aggregate data published from the randomized, controlled Caffeine for Apnea of Prematurity Trial (NCT00182312). FDA reviewed findings from NICHD-2014-CAF01 and the requested labeling changes for Cafcit injection.[2]

On March 2, 2020, FDA approved labeling changes for Cafcit injection that[3]:

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This review was prompted by the March 2, 2020, pediatric labeling changes. DPV has not previously performed a pediatric postmarketing pharmacovigilance review for Cafcit injection for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Cafcit injection labeling contains the following safety information excerpted from the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the Cafcit injection Prescribing Information. For additional Cafcit injection labeling information, please refer to the full prescribing information.[1]

CONTRAINDICATIONS

CAFCIT (caffeine citrate) is contraindicated in patients who have demonstrated hypersensitivity to any of its components.

WARNINGS

Necrotizing Enterocolitis

During the double-blind, placebo-controlled clinical trial, 6 cases of necrotizing enterocolitis developed among the 85 infants studied (caffeine=46, placebo=39), with 3 cases resulting in death. Five of the six patients with necrotizing enterocolitis were randomized to or had been exposed to CAFCIT (caffeine citrate). Reports in the published literature have raised a question regarding the possible association between the use of methylxanthines and development of necrotizing enterocolitis, although a causal relationship between methylxanthine use and necrotizing enterocolitis has not been established. In a published randomized, placebo-controlled, clinical trial that studied the use of caffeine citrate in apnea of prematurity in approximately 2000 patients, necrotizing enterocolitis was not more common in caffeine treated patients compared to placebo. As with all preterm infants, patients being treated with CAFCIT should be carefully monitored for the development of necrotizing enterocolitis.

PRECAUTIONS

General

Apnea of prematurity is a diagnosis of exclusion. Other causes of apnea (e.g., central nervous system disorders, primary lung disease, anemia, sepsis, metabolic disturbances, cardiovascular abnormalities, or obstructive apnea) should be ruled out or properly treated prior to initiation of CAFCIT (caffeine citrate). Caffeine is a central nervous system stimulant and in cases of caffeine overdose, seizures have been reported. CAFCIT should be used with caution in infants with seizure disorders. The duration of treatment of apnea of prematurity in the placebo-controlled trial was limited to 10 to 12 days. The efficacy of CAFCIT for longer periods of treatment has not been established. Safety and efficacy of CAFCIT for use in the prophylactic treatment of sudden infant death syndrome (SIDS) or prior to extubation in mechanically ventilated infants have also not been established.

Cardiovascular

Although no cases of cardiac toxicity were reported in the placebo-controlled trial, caffeine has been shown to increase heart rate, left ventricular output, and stroke volume in published studies. Therefore, CAFCIT should be used with caution in infants with cardiovascular disease.

Renal and Hepatic Systems

CAFCIT should be administered with caution in infants with impaired renal or hepatic function. Serum concentrations of caffeine should be monitored and dose administration of CAFCIT should be adjusted to avoid toxicity in this population. (See CLINICAL PHARMACOLOGY, Elimination and Special Populations.)

Laboratory Tests

Prior to initiation of CAFCIT (caffeine citrate), baseline serum levels of caffeine should be measured in infants previously treated with theophylline, since preterm infants metabolize theophylline to caffeine. Likewise, baseline serum levels of caffeine should be measured in infants born to mothers who consumed caffeine prior to delivery, since caffeine readily crosses the placenta.

In the placebo-controlled clinical trial, caffeine levels ranged from 8 to 40 mg/L. A therapeutic plasma concentration range of caffeine could not be determined from the placebo-controlled clinical trial. Serious toxicity has been reported in the literature when serum caffeine levels exceed 50 mg/L. Serum concentrations of caffeine may need to be monitored periodically throughout treatment to avoid toxicity. In clinical studies reported in the literature, cases of hypoglycemia and hyperglycemia have been observed. Therefore, serum glucose may need to be periodically monitored in infants receiving CAFCIT.

Drug Interactions

Cytochrome P450 1A2 (CYP1A2) is known to be the major enzyme involved in the metabolism of caffeine. Therefore, caffeine has the potential to interact with drugs that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2.

Few data exist on drug interactions with caffeine in preterm neonates. Based on adult data, lower doses of caffeine may be needed following coadministration of drugs which are reported to decrease caffeine elimination (e.g., cimetidine and ketoconazole) and higher caffeine doses may be needed following coadministration of drugs that increase caffeine elimination (e.g., phenobarbital and phenytoin).
Caffeine administered concurrently with ketoprofen reduced the urine volume in four healthy volunteers. The clinical significance of this interaction in preterm neonates is not known.
Interconversion between caffeine and theophylline has been reported in preterm neonates. The concurrent use of these drugs is not recommended.

ADVERSE REACTIONS
Overall, the reported number of adverse events in the double-blind period of the controlled trial was similar for the CAFCIT (caffeine citrate) and placebo groups. The following table shows adverse events that occurred in the double-blind period of the controlled trial and that were more frequent in CAFCIT-treated patients than placebo.

ADVERSE EVENTS THAT OCCURRED MORE FREQUENTLY IN CAFCIT-TREATED PATIENTS THAN PLACEBO DURING DOUBLE-BLIND THERAPY

Adverse Event (AE)	CAFCIT N=46 n (%)	Placebo N=39 n (%)
BODY AS A WHOLE		
Accidental injury	1 (2.2)	0 (0.0)
Feeding intolerance	4 (8.7)	2 (5.1)
Sepsis	2 (4.3)	0 (0.0)
CARDIOVASCULAR SYSTEM		
Hemorrhage	1 (2.2)	0 (0.0)
DIGESTIVE SYSTEM		
Necrotizing Enterocolitis	2 (4.3)	1 (2.6)
Gastritis	1 (2.2)	0 (0.0)
Gastrointestinal Hemorrhage	1 (2.2)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM		
Disseminated Intravascular Coagulation	1 (2.2)	0 (0.0)
METABOLIC AND NUTRITIVE DISORDERS	1 (2.2)	0 (0.0)
Acidosis	1 (2.2)	0 (0.0)
Healing Abnormal		
NERVOUS SYSTEM		
Cerebral Hemorrhage	1 (2.2)	0 (0.0)
RESPIRATORY SYSTEM		
Dyspnea	1 (2.2)	0 (0.0)
Lung Edema	1 (2.2)	0 (0.0)
SKIN AN APPENDAGES		
Dry Skin	1 (2.2)	0 (0.0)
Rash	4 (8.7)	3 (7.7)
Skin Breakdown	1 (2.2)	0 (0.0)
SPECIAL SENSES		
Retinopathy of Prematurity	0 (0.0)	0 (0.0)
UROGENITAL SYSTEM		
Kidney Failure	1 (2.2)	0 (0.0)

In addition to the cases above, three cases of necrotizing enterocolitis were diagnosed in patients receiving CAFCIT (caffeine citrate) during the open-label phase of the study.
Three of the infants who developed necrotizing enterocolitis during the trial died. All had been exposed to caffeine. Two were randomized to caffeine, and one placebo patient was “rescued” with open-label caffeine for uncontrolled apnea.
Adverse events described in the published literature include: central nervous system stimulation (i.e., irritability, restlessness, jitteriness), cardiovascular effects (i.e., tachycardia, increased left ventricular output, and increased stroke volume), gastrointestinal effects (i.e., increased gastric aspirate, gastrointestinal intolerance), alterations in serum glucose (i.e., hypoglycemia and

hyperglycemia), and renal effects (i.e., increased urine flow rate, increased creatinine clearance, and increased sodium and calcium excretion). Published long-term follow-up studies have not shown caffeine to adversely affect neurological development or growth parameters.
A published randomized, placebo-controlled, clinical trial in premature infants with birthweights of 500 1250 grams studied the safety of caffeine citrate in apnea of prematurity (NCT00182312). This trial randomized approximately 2000 premature infants with a mean gestational age of 27 weeks at birth. The median duration of caffeine therapy was 37 days. Prior to discharge home, death, ultrasonographic signs of brain injury, and necrotizing enterocolitis were not more common in the caffeine citrate group compared to the placebo. At follow up at both 18 months and 5 years corrected age, death was not more common in the caffeine citrate treated group compared to placebo, nor did caffeine citrate use adversely affect neurodevelopmental outcomes.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of search	December 12, 2023
Time period of search	September 21, 1999† - December 11, 2023
Search type	RxLogix Pediatric Focused Review Alert
Product terms	Product active ingredient: caffeine citrate
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Cafcit injection approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=new drug application	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

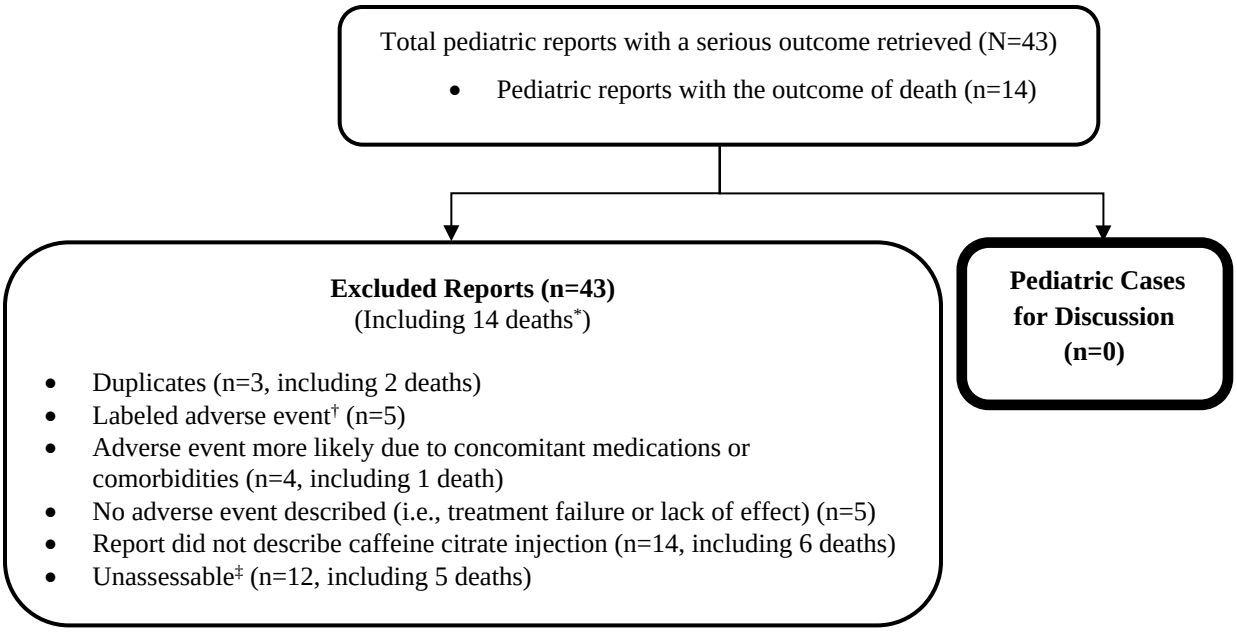
Table 1 presents the number of adult and pediatric FAERS reports from September 21, 1999 - December 11, 2023, with caffeine citrate injection.

Table 1. Total Adult and Pediatric FAERS Reports* Received by FDA from September 21, 1999 – December 11, 2023, with Caffeine Citrate Injection			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	179 (101)	169 (91)	106 (72)
Pediatrics (0 - < 17 years)	49 (37)	43 (31)	14 (12)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 43 serious pediatric reports from September 21, 1999 – December 11, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Caffeine Citrate Injection



* Fourteen excluded FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to caffeine citrate injection. Two reports were duplicates. One case described the death of a neonate born at 24 weeks gestation who had a complicated medical course in the neonatal intensive care unit and whose death was attributed to propylene glycol toxicity. Six cases described fatal outcomes in patients who were not exposed to caffeine citrate injection. Five cases described neonatal and infant deaths but lacked sufficient clinical information to make meaningful causality assessments for caffeine citrate injection.

† Labeled adverse event does not represent increased severity or frequency.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV searched FAERS for all reports with caffeine citrate injection in pediatric patients less than 17 years of age from September 21, 1999 – December 11, 2023, and identified 43 reports. However, all 43 reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths that could be attributed to caffeine citrate injection in pediatric patients less than 17 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for caffeine citrate injection at this time and will continue routine pharmacovigilance monitoring for caffeine citrate injection.

6 REFERENCES

1. Cafcit Injection (caffeine citrate injection, USP). [Prescribing information]. Eatontown, NJ; Hikma Pharmaceuticals USA, Inc.: December 2019.
2. Federal Register. Docket FDA-2019-N-3414. July 19, 2019. Available at: https://www.regulations.gov/document/FDA-2019-N-3414-0001, Accessed on December 21, 2023.
3. Approval Letter. NDA 020793/S-019. March 2, 2020.

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.

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