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

Pediatric Postmarketing Pharmacovigilance

Date:	July 3, 2019
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Product Name:	Calcium gluconate injection
Pediatric Labeling Approval Date:	June 15, 2017
Application Type/Number:	NDA 208418
Applicant/Sponsor:	Fresenius Kabi USA
OSE RCM #:	2019-780

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for calcium gluconate injection in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this safety review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on all unlabeled adverse events associated with calcium gluconate injection in pediatric patients.

The FDA approved calcium gluconate injection on June 15, 2017 and it is indicated for pediatric and adult patients for the treatment of acute symptomatic hypocalcemia. The approved pediatric labeling is for the treatment of acute symptomatic hypocalcemia in ages 0-16 years.
We reviewed all 46 pediatric FAERS reports with calcium gluconate injection in the pediatric population less than 17 years during the period June 15, 2017 through March 19, 2019. Most reports described labeled adverse events such as infusion site reaction, adverse events with compelling alternative explanations (e.g., complications from sepsis or multi-organ failure in advanced neoplastic disease, central intravenous catheter-related infections), or had limited information which precluded a meaningful causality assessment. Of the 46 cases reviewed, we identified a singular case describing an adverse event of interest. The case described nephrocalcinosis with calcium gluconate injection in a patient with complex medical history including DiGeorge syndrome and a history of cardiac surgery with risk factors for nephrocalcinosis including concomitant furosemide and cholecalciferol therapy. The case lacked details to create a robust argument for causality for nephrocalcinosis and calcium gluconate injection. An expanded FAERS search identified no additional pediatric reports and one report describing renal graft nephrocalcinosis in an adult patient with suspected multiple risk factors for the condition. No clear patterns or trends suggested a new safety signal of nephrocalcinosis and calcium gluconate injection at this time.

DPV will continue monitoring for all adverse events associated with the use of calcium gluconate injection including nephrocalcinosis.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) for reports of calcium gluconate injection in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this safety review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on all unlabeled adverse events associated with calcium gluconate injection in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Calcium gluconate injection is a sterile, preservative-free, non-pyrogenic, supersaturated solution of calcium gluconate for intravenous use. It is available as 1,000 mg per 10 mL (100 mg per mL) or 5,000 mg per 50 mL (100 mg per mL) in a single-dose vial, or 10,000 mg per 100 mL (100 mg per mL) in a pharmacy bulk package. Each mL of the drug product contains 100 mg of calcium gluconate (equivalent to 94 mg of calcium gluconate and 4.5 mg of calcium saccharate tetrahydrate), hydrochloric acid and/or sodium hydroxide for pH adjustment (6.0 to 8.2), and sterile water for injection. Each mL of calcium gluconate injection contains 9.3 mg (0.465 mEq) elemental calcium.[1]

FDA approved calcium gluconate on June 15, 2017.[2] Calcium gluconate is indicated for pediatric and adult patients for the treatment of acute symptomatic hypocalcemia. The approved pediatric labeling is for the treatment of acute symptomatic hypocalcemia in ages 0-16 years.[1] Prior to FDA approval, the Sponsor marketed calcium gluconate as an unapproved drug in the U.S. based on the contention that calcium gluconate met the "grandfathered" status being originally marketed before the enactment of the 1938 and 1962 grandfather laws.[3,4] In 2006, FDA issued the Guidance for FDA Staff and Industry: Marketed Unapproved Drugs – Compliance Policy Guide, recommending that all marketed drugs must obtain FDA approval.[4] Subsequently, this lead to the Sponsor's submission of the Pre-IND briefing package on October 2011 to seek regulatory guidance from FDA on the new drug application process for calcium gluconate.[3]

Efficacy and safety data for the pediatric approval of calcium gluconate injection, including dosing recommendation, are based on clinical and nonclinical data from the scientific published literature and clinical experience. The Division of Metabolism and Endocrinology Products (DMEP) determined that it was not ethical to conduct a placebo control trial nor feasible to conduct a comparative trial with an approved therapy because calcium chloride also obtained approval by relying on the medical literature, without adequate and well-controlled studies. Below are the efficacy and safety summaries for calcium gluconate.[3]

Efficacy:[3]

- In one randomized, controlled trial of adult patients, an acute bolus of calcium gluconate 30 mg/kg rapidly increased serum ionized calcium levels. In non-randomized studies, repeated boluses or infusions delivering 1000 to 4000 mg per day increased or maintained serum ionized calcium levels in patients with acute, symptomatic

hypocalcemia. Review articles and guidelines support dosing recommendations for continuous infusions of 5.4 to 21.5 mg/kg/hour in adult patients with acute, symptomatic hypocalcemia.

- In a randomized, controlled trial of pediatric patients with hypocalcemia, a bolus dose of calcium gluconate 29 mg/kg rapidly increased serum ionized calcium levels. In case reports, single boluses up to 90 mg/kg and repeated boluses or continuous infusions providing cumulative doses up to 300 mg/kg/day increased ionized or total serum calcium in pediatric patients, greater than 1 month and less than 17 years, with hypocalcemia. Guidelines support single bolus doses up to 60 mg/kg.
- Among studies involving only neonatal patients, ages less than or equal to one month, three randomized, controlled trials and several non-randomized studies provided evidence that a single bolus of calcium gluconate 100 to 200 mg/kg increases serum ionized calcium after one to eight hours, and that repeated boluses or continuous infusions delivering 400 to 800 mg/kg/day, increase serum ionized calcium over 24 hours. Reviews and guidelines also support these doses.

Safety:[3,5]

- Cardiac events are the most serious adverse reactions associated with calcium gluconate infusion. Rapid injection of calcium gluconate may cause bradycardia, decreased blood pressure, cardiac arrhythmias (including atrial fibrillation, atrioventricular block, and asystole), and cardiac arrest.
- The most common adverse reactions associated with calcium gluconate reported in the literature are skin and soft tissue reactions, primarily calcinosis cutis and skin necrosis. The majority of the reports of calcinosis cutis and other skin reactions occurred in neonates. Skin necrosis is the most commonly reported complication of calcinosis cutis.
- 2007 and 2009 Drug Safety Communications (DSCs) alerted healthcare professionals of reports of fatal cases in neonates who had received simultaneous administration of ceftriaxone and calcium-containing products and the in vitro studies conducted in neonatal and adult plasma looking for ceftriaxone-calcium precipitates using varying concentrations of both drugs. The DSC noted that administration of the two products at different times and via different infusion lines has been fatal in neonates 28 days of age or younger.

DPV has not presented postmarketing adverse event reports for calcium gluconate injection in pediatric patients before the Pediatric Advisory Committee in the past. Currently, there are no pending tracked safety issues (TSIs), specific safety issues that are being monitored, or possible labeling changes that may take place prior to the September 2019 PAC.

1.2 RELEVANT LABELED SAFETY INFORMATION

Below is the relevant labeling safety information for calcium gluconate[2]:

4 CONTRAINDICATIONS

Calcium gluconate Injection is contraindicated in:

- Hypercalcemia
- Neonates (28 days of age or younger) receiving ceftriaxone *[see Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Arrhythmias with Concomitant Cardiac Glycosides Use

Cardiac arrhythmias may occur if calcium and cardiac glycosides are administered together. Hypercalcemia increases the risk of digoxin toxicity. Administration of Calcium Gluconate Injection should be avoided in patients receiving cardiac glycosides. If concomitant therapy is necessary, Calcium Gluconate Injection should be given slowly in small amounts and with close ECG monitoring *[see Drug Interactions (7.1)]*.

5.2 End-Organ Damage due to Intravascular Ceftriaxone-Calcium Precipitates

Concomitant use of ceftriaxone and Calcium Gluconate Injection is contraindicated in neonates (28 days of age or younger) due to cases of fatal outcomes in neonates in which a crystalline material was observed in the lungs and kidneys at autopsy after ceftriaxone and calcium were administrated simultaneously through the same intravenous line. Concomitant administration can lead to the formation of ceftriaxone-calcium precipitates that may act as emboli, resulting in vascular spasm or infarction *[see Contraindications (4)]*.

In patients older than 28 days of age, ceftriaxone and Calcium Gluconate Injection may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid. Do not administer Ceftriaxone simultaneously with Calcium Gluconate Injection via a Y-site in any age group.

5.3 Tissue Necrosis and Calcinosis

Intravenous administration of Calcium Gluconate Injection and local trauma may result in calcinosis cutis due to transient increase in local calcium concentration. Calcinosis cutis can occur with or without extravasation of Calcium Gluconate Injection, is characterized by abnormal dermal deposits of calcium salts, and clinically manifests as papules, plaques, or nodules that may be associated with erythema, swelling, or induration. Tissue necrosis, ulceration, and secondary infection are the most serious complications.
If extravasation occurs or clinical manifestations of calcinosis cutis are noted, immediately discontinue intravenous administration at that site and treat as needed.

5.4 Hypotension, Bradycardia, and Cardiac Arrhythmias with Rapid Administration

Rapid injection of Calcium Gluconate Injection may cause vasodilation, decreased blood pressure, bradycardia, cardiac arrhythmias, syncope and cardiac arrest. To avoid adverse reactions that may follow rapid intravenous administration, Calcium Gluconate Injection should be diluted with 5% dextrose or normal saline and infused slowly. If rapid intravenous bolus of Calcium Gluconate Injection is required, the rate of intravenous administration should not exceed 200 mg/minute in adults and 100 mg/minute in pediatric patients and ECG monitoring during administration is recommended *[see Dosage and Administration (2.1)]*.

5.5 Aluminum Toxicity

Calcium Gluconate Injection contains aluminum, up to 400 mcg per liter, that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 mcg/kg/day to 5 mcg/kg/day accumulate aluminum levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

8 USE IN SPECIAL POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Calcium Gluconate Injection have been established in pediatric patients for the treatment of acute, symptomatic hypocalcemia.
Pediatric approval for Calcium Gluconate Injection, including doses, is not based on adequate and well-controlled clinical studies. Safety and dosing recommendations in pediatric patients are based on published literature and clinical experience *[see Dosage and Administration (2.2)]*.
Concomitant use of ceftriaxone and Calcium Gluconate Injection is contraindicated in neonates (28 days of age or younger) due to reports of fatal outcomes associated with the presence of lung and kidney

ceftriaxone-calcium precipitates. In patients older than 28 days of age, ceftriaxone and Calcium Gluconate Injection may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid [*see Contraindications (4) and Warnings and Precautions (5.2)]*. This product contains up to 400 mcg/L aluminum which may be toxic, particularly for premature neonates due to immature renal function. Parenteral administration of aluminum greater than 4 to 5 mcg/kg/day is associated with central nervous system and bone toxicity *[see Warnings and Precautions (5.5)]*.

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	03/20/2019
Time Period of Search	06/15/2017† - 03/19/2019
Search Type	FBIS: Product-Manufacturer Reporting Summary
Product Terms	Product active ingredient: calcium gluconate
MedDRA Search Terms (Version 21.1)	All PT terms
* See Appendix A for a description of the FAERS database. † U.S. Approval Date and Pediatric Labeling Change Date	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from June 15, 2017 through March 19, 2019 with calcium gluconate injection.

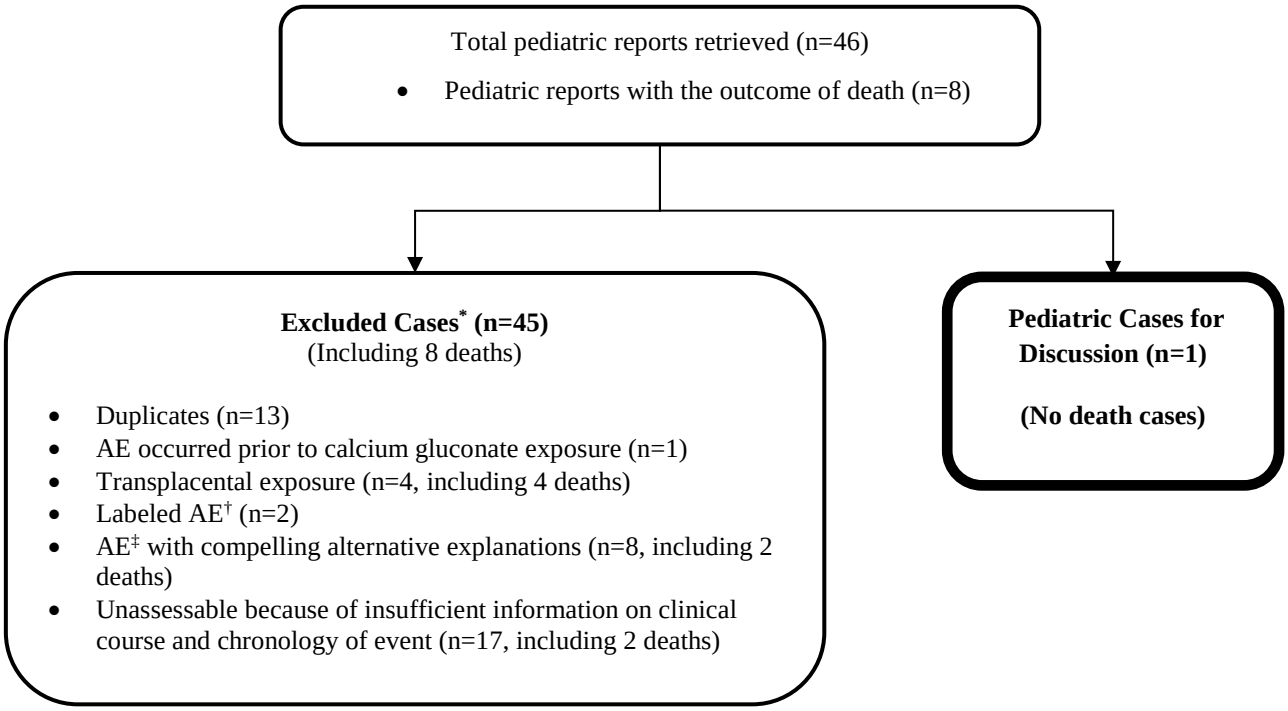
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from June 15, 2017 through March 19, 2019 with Calcium Gluconate Injection			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	69 (14)	65 (11)	34 (3)
Pediatrics (0 - <17 years)	46‡ (3)	**46‡ (3)**	8‡ (1)
* May 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, and other serious important medical events. ‡ Four additional cases of pediatric deaths were identified among reports not reporting an age. These reports are included in the counts for pediatric deaths. See Figure 1.			

3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved 46 pediatric reports from June 15, 2017 through March 19, 2019.

We reviewed all FAERS pediatric reports. We excluded reports from further discussion for various reasons, such as if the adverse event was unlikely to be causally related to the use of calcium gluconate (e.g., the report provided compelling alternative explanations such as sepsis and multi-organ failure from advanced neoplastic disease, central intravenous catheter-related infections), duplicates, transplacental exposure, labeled adverse events, and insufficient clinical information for causality assessment. We summarize the one remaining case in the sections below. Figure 1 presents the selection of cases for further discussion.

Figure 1. Selection of Pediatric Cases with Calcium Gluconate



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above
† Labeled AEs include infusion site reaction (n=1), tissue necrosis following intravenous catheter infiltration (n=1)
‡ AEs include sepsis and multi-organ failure from advanced neoplastic disease leading to death (n=2), blood in stool in a patient with enterocolitis infection (n=1), foot cyanosis secondary to thrombosis (n=1), ventricular fibrillation from ammonium bifluoride poisoning (n=1), and central intravenous catheter-related infections in patients dependent on parenteral nutrition (n=3; isolates included mixed gram positive and gram negative organisms in a patient with a history of recurrent central line infections with the same organisms n=1, Lactobacillus paracasei n=1, and Pantoea bacterium n=1).

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not include any fatal pediatric adverse event reports for further discussion (see Figure 1 for reasons for exclusion).

3.1.4 Summary of Non-Fatal Pediatric Cases (N=1)

We identified one foreign case associated with a serious outcome describing an unlabeled adverse event of nephrocalcinosis in a pediatric patient receiving calcium gluconate. The narrative summary is available below:

FAERS# 14391432v2/MFR# HU-VALIDUS PHARMACEUTICALS LLC-HU-2018VAL000115/Expedited/Hungary/January 2018

A pharmacist reported a 3-month-old male patient who received calcium gluconate at an unknown dose and frequency for hypocalcemia (baseline blood calcium was 6.72 mg/dL) developed nephrocalcinosis. The patient's medical history included DiGeorge syndrome, coarctation of the aorta, bicuspid aortic valve, patent ductus arteriosus, congenital ventricular septal defect, congenital hydronephrosis, pyelocaliectasis, hypocalcemia, phrenic nerve paralysis, reflux esophagitis, bronchostenosis, unilateral complete paralysis of vocal cords, severe combined immunodeficiency syndrome, and history of cardiac surgery. Concomitant medications included ophthalmic neomycin, fenoterol/ipratropium, domperidone, sulfamethoxazole/trimethoprim, ursodiol, folic acid, pantoprazole, and colecalciferol. Approximately 75 days after starting furosemide (unknown dose and frequency) and calcium gluconate and 60 days after starting calcium lactate (unknown dose and frequency), the patient was diagnosed with nephrocalcinosis via ultrasound. The kidney ultrasound showed initial stages of nephrocalcinosis along the edges of the renal pyramids. The reporter did not provide the clinical outcomes and action taken for suspected products (furosemide, calcium gluconate, and calcium lactate).

Reviewer's comments: Nephrocalcinosis describes the deposition of calcium oxalate and calcium phosphate in renal tissue secondary to an increase in urinary excretion of calcium, phosphate, or oxalate. The most common cause of nephrocalcinosis is increased urinary calcium excretion with or without hypercalcemia.[6] Hypocitraturia may also contribute to nephrocalcinosis as citrate normally inhibits crystal formation by forming a soluble calcium complex.[6] Neonates with low birth weight or prematurity are at risk for developing nephrocalcinosis.[7] Additional risk factors for nephrocalcinosis include primary hyperparathyroidism, vitamin D therapy, inherited tubulopathies, and chronic hypokalemia. The most common clinical setting for nephrocalcinosis is in premature infants and in infants who receive furosemide or corticosteroids who receive longer periods of parenteral nutrition.[8] This report confirms the patient's prolonged exposure to furosemide, which is labeled for nephrocalcinosis, and the complex history and cardiac surgery implies potential prolonged exposure to parenteral nutrition. DiGeorge syndrome is associated with hypocalcemia secondary to hypoparathyroidism and in this setting, the goal for treatment is to maintain calcium levels in the low normal range (8-9mg/dL) as higher levels result in hypercalciuria due to the loss of renal calcium-retaining effects of parathyroid hormone.[9,10] The case offers no information about the patient's monitored calcium concentrations during calcium supplementation, information on urinary calcium excretion and urinalysis, nor does it contain information cholecalciferol dosing and vitamin D levels, which would contribute to the causal analysis between calcium gluconate and nephrocalcinosis. For completeness, we performed a separate FAERS search for nephrocalcinosis and calcium gluconate in adult patients since

approval; the search retrieved one report (FAERS 9303500v1) that described a 49-year-old female with a history renal transplant due to unspecified renal failure and hyperparathyroidism status post-parathyroidectomy who developed graft nephrocalcinosis due to calcium, potassium phosphate, and vitamin D supplementation. An additional search for nephrocalcinosis in pediatric FAERS reports with calcium gluconate since approval did not retrieve additional reports.

4 DISCUSSION

We reviewed all 46 pediatric FAERS reports with calcium gluconate injection in the pediatric population less than 17 years during the period June 15, 2017 through March 19, 2019. Most reports described labeled adverse events such as infusion site reaction, adverse events with compelling alternative explanations (e.g., complications from sepsis or multi-organ failure in advanced neoplastic disease, central intravenous catheter-related infections), or had limited information which precluded a meaningful causality assessment. Of the 46 cases reviewed, we identified a singular case describing an adverse event of interest. The case described nephrocalcinosis with calcium gluconate injection in a patient with complex medical history including DiGeorge syndrome and a history of cardiac surgery with risk factors for nephrocalcinosis including concomitant furosemide and cholecalciferol therapy. The case lacked details to create a robust argument for causality for nephrocalcinosis and calcium gluconate injection. An expanded FAERS search identified no additional pediatric reports and one report describing renal graft nephrocalcinosis in an adult patient with suspected multiple risk factors for the condition. No clear patterns or trends suggested a new safety signal of nephrocalcinosis and calcium gluconate injection at this time.

5 CONCLUSION

We identified one adverse event of interest, nephrocalcinosis, with calcium gluconate injection use. However, there is insufficient evidence to suggest this is a new safety signal at this time**.**

6 RECOMMENDATION

DPV will continue monitoring for all adverse events associated with the use of calcium gluconate injection including nephrocalcinosis.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 tradenames 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.

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