CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208418
Priority or Standard	Standard
Submit Date(s)	May 16, 2016
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Division / Office	Division of Metabolism and Endocrinology Products
Reviewer Name(s)	John Sharretts, M.D.
Review Completion Date	May 26, 2017
Established Name	Calcium Gluconate
(Proposed) Trade Name	Calcium Gluconate Injection
Therapeutic Class	Calcium
Applicant	Fresenius Kabi
Formulation(s)	Injection
Dosing Regimen	100 mg/mL in 10, 50, and 100 mL vials
Indication(s)	Acute, symptomatic hypocalcemia
Intended Population(s)	Adult and pediatric patients with acute, symptomatic hypocalcemia

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of the application for Calcium Gluconate Injection for the treatment of acute, symptomatic hypocalcemia

1.2 Risk Benefit Assessment

Acute hypocalcemia is a potentially fatal electrolyte disorder. Symptoms and clinical consequences depend on the magnitude and acuity of the decrease in serum calcium levels. Symptomatic hypocalcemia may lead to severe complications, and for most causes of acute hypocalcemia, decreased serum ionized calcium concentrations and associated symptoms of hypocalcemia cannot remit spontaneously without resolution of the underlying disorder.

Intravenous infusion of calcium gluconate rapidly increases the serum ionized calcium concentration above the symptom threshold. The effect on serum ionized calcium levels in small studies is consistent across adult, pediatric, and neonatal populations.

The most serious risks associated with parenteral calcium infusion are arrhythmias, myocardial depression, and cardiac arrest associated with rapid infusion. Appropriate selection of patients (those with acute, symptomatic hypocalcemia), proper administration with a slow infusion rate, and cardiac monitoring during infusion mitigate these risks.

The most common adverse reactions associated with calcium gluconate infusion include local skin and soft tissue disorders, including soft tissue inflammation, calcinosis cutis, and skin necrosis. Dilution of the drug product, slow infusion rate, infusion through a secure intravenous line, and rotation of intravenous sites mitigate these risks.

In patients with acute, symptomatic hypocalcemia, the benefits of acute therapy with intravenous calcium gluconate outweigh any potential risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

Hypocalcemia is a potentially fatal electrolyte disorder that occurs in about 15% of hospitalized patients, and up to 85% of patients in intensive care.[1] Symptoms and clinical consequences depend on the magnitude and acuity of the decrease in serum calcium levels,[2] ranging from an asymptomatic laboratory finding to serious metabolic disorders.[1]

Symptoms of hypocalcemia include paresthesia, muscle cramps, muscle weakness, myalgia, dysphagia, irritability, depression, and confusion. Physical signs include hyperreflexia and carpopedal spasm. Severe, acute hypocalcemia may result in serious complications, such as hypotension, myocardial dysfunction, cardiac arrhythmias, bronchospasm, laryngospasm, and seizures. These complications are most likely to occur in symptomatic patients or asymptomatic patients with total serum calcium less than 7.6 mg/dL (1.9 mmol/L) or ionized calcium less than 2.8 mg/dL (0.7 mmol/L).[1,2]

Calcium regulates many intracellular and extracellular processes, including hormone secretion, muscle function, coagulation, enzyme activity, cell division, and membrane stability.[3] Over 99% of total body calcium is stored in the bone, and less than 1% is exchangeable with extracellular fluid. 40% of circulating calcium is protein bound, 8-10% is complexed with organic and inorganic anions, and about 50% is ionized. Ionized calcium is the metabolically active form.[2,4]

Normal calcium homeostasis requires a narrow therapeutic range. Parathyroid hormone (PTH), vitamin D, and calcium itself are the major hormonal regulators of serum calcium concentration. Activation of the calcium sensing receptor (CaSR) by elevated serum calcium results in decreased PTH secretion by the parathyroid glands and increased calcium excretion in the loop of Henle in the kidney.[5] Decreased serum calcium results in increased PTH secretion, which stimulates bone resorption, decreases calcium excretion by the kidney by stimulating reabsorption in the distal tubule, and increases intestinal calcium absorption indirectly via increased kidney production of 1,25-dihydroxyvitamin D (calcitriol), the most active form of vitamin D.

1 Cooper. *BMJ* 2008; 336(7656):1298-1302
2 French. *South Med J* 2012; 105(4):231-237
3 Zaloga. *Crit Care Med* 1992; 20(2):251-262
4 Kelly. *J Intensive Care Med* 2013; 28(3):166-177
5 Riccardi. *Am J Physiol Renal Physiol* 2010; 298: F485–F499

Hypocalcemia generally occurs due to either disruption of the hormonal pathways (decreased secretion of PTH, vitamin D deficiency, or decreased action of either hormone) or rapid removal of calcium from the circulation (chelation, rapid extracellular deposition):

- Decreased PTH secretion (hypoparathyroidsm) results from autoimmune destruction, surgical removal, or congenital absence of the parathyroid glands.
- Vitamin D deficiency may be caused by decreased dietary intake or malabsorption of vitamin D combined with decreased exposure to ultraviolet light, impaired hydroxylation of vitamin D to its more active forms (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) due to liver or kidney disease, or increased metabolism of vitamin D to inactive metabolites caused by antiepileptic drugs and other inducers of cytochrome P-450 enzymes.
- PTH resistance (pseudohypoparathyroidism) and vitamin D resistance are rare conditions caused by genetic mutations of the receptors for these hormones or their signaling pathways. Bone antiresorptive medications (bisphosphonates and denosumab) inhibit PTH-mediated osteoclast proliferation or action.
- Chelating agents, such as citrate, lactate, foscarnet, and sodium ethylenediaminetetraacetic acid (EDTA), reduce serum ionized calcium concentrations without affecting the total serum calcium level. Hyperphosphatemia, osteoblastic metastases, and acute pancreatitis are the most common causes of extravascular calcium deposition.
- Hypocalcemia due to critical illness is multifactorial, including impaired PTH secretion, decreased calcitriol production, and resistance to PTH.
- Hypomagnesemia causes hypocalcemia by suppressing PTH secretion and inducing PTH resistance.[1,2,3]

Acute decreased serum ionized calcium concentrations cannot remit spontaneously without resolution of the underlying condition. In the case of PTH deficiency or resistance, bone calcium stores are inaccessible. In vitamin D deficient states, impaired gastrointestinal absorption is accompanied by bone demineralization (lack of calcium stores). Chelation or precipitation removes calcium from the circulation more rapidly than physiologic processes can replace it.

2.1 Product Information

Calcium Gluconate Injection (Fresenius Kabi USA) is a sterile, preservative-free, non-pyrogenic, supersaturated solution of calcium gluconate for intravenous use. 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, q.s. Each mL of Calcium Gluconate Injection contains 9.3 mg elemental calcium (0.465

mEq). The chemical formula is $C_{12}H_{22}CaO_{14}$, and the molecular weight is (b) (4) grams per mole.

2.2 Tables of Currently Available Treatments for Proposed Indications

10% Calcium Chloride Injection, USP (NDA 021117, Hospira) is approved for the treatment of hypocalcemia in those conditions requiring a prompt increase in plasma calcium levels. Calcium Gluconate Injection, USP 10% (Fresenius Kabi US, American Regent, Inc.) is a marketed unapproved drug, used for the treatment of conditions arising from calcium deficiencies such as hypocalcemic tetany, hypocalcemia due to hypoparathyroidism, and hypocalcemia due to rapid growth or pregnancy. It is also used in the treatment of black widow spider bites, and as an adjunct in the treatment of rickets, osteomalacia, lead colic, and magnesium sulfate overdosage.

2.3 Availability of Proposed Active Ingredient in the United States

Calcium Gluconate Injection, USP 10% is a marketed, unapproved drug. 10% Calcium Chloride Injection USP (NDA 021117) is approved for the treatment of hypocalcemia in those conditions requiring a prompt increase in plasma calcium levels. Calcium chloride is an active ingredient of several approved injectable products, including Clinimex E (NDA 020678, Baxter Healthcare), Deleflex with Dextrose (NDA 018883, Fresenius Medical), Ringer's, and Lactated Ringers (Multiple approved formulations: Baxter Healthcare, ICU Medical, B Braun, Abbott). Calcium is available as an oral dietary supplement as various salts, including calcium carbonate, calcium citrate, calcium gluconate, calcium lactate, and calcium phosphate.

2.4 Important Safety Issues With Consideration to Related Drugs

Adverse reactions listed in the prescribing information of 10% Calcium Chloride Injection USP include necrosis and sloughing associated with direct injection into perivascular tissues, potential for aluminum toxicity with prolonged administration, peripheral vasodilation, decreased blood pressure, and burning sensation associated with peripheral infusion.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant, Fresenius Kabi US, currently markets Calcium Gluconate Injection, USP 10% as an unapproved drug, and is also the Sponsor for the IND (113171) associated with this application through its subsidiary, APP Pharmaceuticals LLC. The Sponsor requested a pre-IND meeting on August 19, 2011. The Division granted the request and

provided preliminary comments on November 15, 2011. Questions included the need for additional non-clinical or clinical studies to support a 505(b)(2) application relying on the published medical literature, the adequacy of the data to support a pediatric indication, the adequacy of clinical pharmacology data, and the adequacy of the stability data set. The Sponsor accepted the Division's responses and canceled the pre-IND meeting.

The Sponsor submitted an initial pediatric study plan (iPSP) on July 27, 2015. The Division requested that the Sponsor submit additional data from additional searches of the literature and pediatric electronic databases to support safety in the pediatric population, ages greater than one month to less than 17 years. The Sponsor and the Division reached agreement on the iPSP on April 13, 2016.

The Applicant submitted this application on May 16, 2016. The Division completed the filing review and classified the application as Standard, with an original user fee goal date of March 16, 2017. The filing review identified several potential Chemistry, Manufacturing, and Controls (CMC) review issues, and one potential clinical review issue regarding safety data in the pediatric population greater than one month. The Applicant submitted a major amendment to the application addressing the CMC issues, and on February 23, 2017 the Division extended the user fee goal date by three months to June 16, 2017.

2.6 Other Relevant Background Information

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the FD&C Act), requiring approval of new drugs for safety. In 1962, Congress amended the Act to require that a new drug also be proven effective, as well as safe, to obtain FDA approval. The 1938 grandfather clause exempted certain drug products on the market prior to passage of the 1938 Act from the requirement of having an approved new drug application, and the 1962 grandfather clause exempted certain drug products from the effectiveness requirement. Believing that very few unapproved drugs on the market were entitled to grandfather status, in 2011 the FDA issued the *Guidance for FDA Staff and Industry: Marketed Unapproved Drugs—Compliance Policy Guide*, recommending that all marketed drugs must obtain FDA approval.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant organized the submission appropriately and provided all supportive literature. The Application does not contain reviewable patient data.

3.2 Compliance with Good Clinical Practices

The Applicant did not conduct any clinical studies.

3.3 Financial Disclosures

The Applicant did not submit financial disclosure information, because the application did not reference any clinical studies conducted by or funded by the Applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the Product Quality Review

4.2 Clinical Microbiology

Refer to the Product Quality Review

4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology/Toxicology Review by Arunsalam Thilagar

4.4 Clinical Pharmacology

Refer to the Clinical Pharmacology Review by Renu Singh

4.4.1 Mechanism of Action

Intravenous infusion of calcium gluconate increases serum ionized calcium in patients with hypocalcemia. Calcium is a major regulator of many intracellular and extracellular processes, including muscle contraction, hormone secretion, enzyme activation, cell division, blood coagulation, membrane stability, and bone structure.

4.4.2 Pharmacodynamics

Intravenous calcium rapidly increases the serum ionized calcium level above the symptom threshold. Refer to the Clinical Pharmacology review for complete discussion.

4.4.3 Pharmacokinetics

Refer to the Clinical Pharmacology Review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 in Section 6 of this review summarizes literature submitted in support of efficacy. Table 13 in Section 7 of this review summarizes literature submitted in support of safety.

5.2 Review Strategy

This reviewer considered all articles submitted by the Applicant individually. In addition, this reviewer also used information from independent searches of the published medical literature and medical textbooks to supplement the determination of efficacy and safety of the product for the proposed indication.

5.3 Discussion of Individual Studies/Clinical Trials

The Applicant did not conduct any trials in support of the application. This review discusses data derived from the published literature in the Reviews of Efficacy and Safety (Sections 6 and 7).

6 Review of Efficacy

Efficacy Summary

The Applicant submitted randomized, controlled trials, prospective non-randomized studies, retrospective studies, case studies, and review articles in support of efficacy Most of the clinical studies and case reports the Applicant submitted used serum ionized calcium or serum total calcium values to document efficacy. In some studies, the authors reported on patient symptoms or physical signs.

In one randomized, controlled trial of adult patients, an acute bolus of calcium gluconate (b) (4) *rapidly increased serum ionized calcium levels. In non-randomized studies, repeated boluses or infusions delivering 1000 to* (b) (4) *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 (b) (4) *and repeated boluses or continuous infusions providing cumulative doses up to* (b) (4) *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.

The application does not meet regulatory standards for study design, data collection, or analyses, but factors specific to this product mitigate the defects. Calcium gluconate is widely used in clinical care. It is probably not ethical or feasible to conduct adequate and well-controlled trials in the proposed population. The risk of serious complications in patients with acute, symptomatic hypocalcemia is too great to support a placebo control trial, and the lack of efficacy data from adequate and well-controlled trials limits use of calcium chloride as an active comparator.

Measurement of serum ionized calcium before and after infusion of calcium gluconate is a valid clinical outcome because clinical symptoms and signs are closely associated with serum ionized calcium levels. Multiple studies in different patient populations

consistently demonstrated that calcium gluconate increased serum ionized calcium, and several of these studies demonstrated improvement in symptoms or signs of hypocalcemia, including tetany, seizures, and atrioventricular block. The clinical studies submitted fulfill the purpose of investigations, to distinguish the effect of calcium gluconate from other influences such as spontaneous change in the course of the disease, placebo effect, or biased observation as defined in 21CFR §314.126(a).

6.1 Indication

The Applicant proposes the following wording in Section 1—*Indications and Usage* of the prescribing information:

> *Calcium Gluconate Injection is indicated for* (b) (4) *.*

This review focuses on the literature supporting the use of intravenous calcium gluconate for the (b) (4) . Other symptoms of hypocalcemia may include paresthesia, muscle cramps, muscle weakness, dysphagia, irritability, depression confusion, seizures, bronchospasm, laryngospasm, and symptoms of cardiac complications such as hypotension, myocardial dysfunction, or arrhythmias.[1,2] In particular, premature neonates usually present with non-specific symptoms such as jitteriness, irritability, and an exaggerated startle reflex, and typically do not exhibit signs of tetany due to decreased overall tone.[6,7]

6.1.1 Methods

Table 1 summarizes literature submitted by the Applicant in support of efficacy, including randomized, controlled trials, prospective non-randomized studies, retrospective studies, case studies, and review articles. Immediately following the table, this review discusses several of the articles that provide the most significant evidence to support efficacy. The discussion includes case reports of pediatric patients, ages greater than one month to less than 17 years, due to the paucity of data in this population. This review omits sections from the standard template that are not applicable to a 505(b)(2) application relying entirely on published literature.

Most of the clinical studies and case reports the Applicant submitted used serum ionized calcium or serum total calcium values to document efficacy. In some studies, the authors reported on patient symptoms or physical signs, including vital signs,

6 Jain. *Indian J Pediatr* 2010; 77(10):1123-1128
7 Mimouni. *J Am Coll Nutr* 1994; 13(5):408-415

physical examination, and ECG to demonstrate clinical improvement. Some studies reported improvement in clinical symptoms or signs without documentation of the change in serum calcium levels.

6.1.2 Demographics

The Applicant summarized demographic data from the submitted articles. Not all articles provided complete information regarding patients' age or sex. For pediatric dosing, if an article provided patient age, but no weight or weight-based dosing, this review estimated the weight-based dose using the median weight for patient's age from published growth charts. The vast majority of articles did not provide information regarding race.

> *Reviewer comment:*
> *Because none of the submitted articles reported individual patient data, it is not possible to reproduce any of the reported statistical analyses or conduct additional analyses.*
>
> *Although some of the studies were uncontrolled, this reviewer considers comparison to baseline as a type of historical control as defined in 21CFR §314.126(b)(2)(v). The natural history of hypocalcemia is predictable. That is, serum calcium does not increase spontaneously absent resolution of the underlying cause (for example, PTH deficiency, PTH resistance, or decreased calcitriol production). In this specific setting, the effect of calcium gluconate infusion on serum calcium levels and symptoms of hypocalcemia is self-evident.*

Table 1: Clinical Efficacy Studies

Clinical Efficacy Studies in Adult Patients				
Source	**Study Design and Population**	**Dose: Calcium Gluconate**	**Dose: Elemental Calcium**	**Efficacy Results**
Buchta 2003	Randomized, placebo controlled trial Adult patients undergoing apheresis: 24 calcium gluconate vs 25 placebo	Infusion: 3844 mg/day **(769 mg/hour)** over 5 hours (mean) during procedure	357 mg/day 71.5 mg/hour over 5 hours	Infusion mitigated the decrease in ionized calcium compared to placebo (10.4% versus 26.9% decrease from baseline). Patients receiving calcium gluconate had lower symptom scores compared to placebo
[redacted] (b) (4)				

Bold text in dose columns indicates doses described in the article text.

(b) (4)

[redacted]

Phebra 2013	Australian prescribing information	Bolus: 1500-3000 mg	**7-14 mEq** (140-280 mg)	No efficacy data

	Different formulation: 1 mL = 8.9 mg elemental calcium 0.22 mmol 0.44 mEq	Infusion: 4800 mg/day **(200 mg/min x 24 hours)** Maximum daily dose: **15 grams/day**	 432 mg/day **Up to 0.9 mEq/min** 18 mg/min **67.5 mEq/day** 1353 mg/day	

Clinical Efficacy Studies in Pediatric Patients (> 1 month to < 17 years)				
Source	**Study Design and Population**	**Dose: Calcium Gluconate**	**Dose: Elemental Calcium**	**Efficacy Results**
Broner 1984	Randomized, controlled trial Pediatric intensive care patients with hypocalcemia 20 calcium gluconate vs 17 calcium chloride	Bolus: **29 mg/kg** Calcium chloride: 10 mg/kg	2.7 mg/kg 2.7 mg/kg	Increased ionized calcium 0.36 mg/dL at 30 minutes Calcium chloride increased ionized calcium by 0.76 mg/dL (0.19 mmol/L) at 30 minutes
[redacted] (b) (4)				

		1000 mg/unit **1000 mg**/unit plus **250 mg/L** circulating blood volume	93 mg/unit 93 mg/unit plus 23.2 mg/L	
(b) (4)				
Helikson 1997	Case report 3-year-old (18 kg) with hypocalcemia due to hyperphosphatemia	<u>Bolus</u>: 55 mg/kg **(1000 mg)** over 10-15 minutes x 2 doses	5.2 mg/kg 93 mg X 2 doses	Ionized calcium increased 1 mg/dL at 6 hours
(b) (4)				

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(b) (4)

[redacted]

Academy of Pediatrics 1998		**60 mg/kg**	5.6 mg/kg	

(b) (4)

Clinical Efficacy Studies in Neonatal Patients (≤ 1 month)				
Source	**Study Design and Population**	**Dose: Calcium Gluconate**	**Dose: Elemental Calcium**	**Efficacy Results**

(b) (4)

Scott 1984	Partly randomized, controlled trial Neonates in intensive care with hypocalcemia 9 Bolus 9 Infusion 9 No treatment	 Bolus: 800 mg/kg/day **(200 mg/kg at 100 mg/min x 4 doses)** Infusion: **400 mg/kg/day**	 74.4 mg/kg/day 37.2 mg/kg/day	At 24 hours, ionized calcium increased: 0.72 mg/dL (0.18 mmol/L) 0.3 mg/dL (0.08 mmol/L)
Bifano 1989	Randomized crossover study Neonates with persistent pulmonary hypertension of the newborn and hypocalcemia 10 subjects calcium vs placebo (saline)	Bolus: **200 mg/kg** over 2 minutes	18.6 mg/kg	Total calcium increased by 2.1 mg/dL and ionized by 1.1 mg/dL above baseline at 55 minutes
Mirro 1984	Randomized crossover study Preterm neonates with hypocalcemia 16 subjects vs placebo (saline)	Bolus: **200 mg/kg** over 2 minutes	18.6 mg/kg	No calcium efficacy data (echo parameters only)
Venkataraman 1985b	Single arm study Preterm neonates less than weeks gestational age and serum calcium < 6.0 mg/dL 8 subjects	Bolus: 200 mg/kg	**18 mg/kg** over 10 min	Total calcium increased 1.9 mg/dL and ionized calcium 0.4 mg/dL (0.1 mmol/L) at 8 hours

Brown 1982	Single arm study Neonates in ICU with total calcium < 7.0 mg/dL 24 subjects	Bolus: **200 mg/kg** over 2 min	18 mg/kg	Total calcium increased 0.9 mg/dL and ionized calcium 0.4 mg/dL (0.1 mmol/L) at 5 hours
Salsburey 1982	Single arm study Preterm neonates with hypocalcemia 24 subjects	Bolus: **200 mg/kg** at 100 mg/min	18.6 mg/kg elemental	No calcium efficacy data (vital signs data only)
[redacted]				(b) (4)
Fishbein 1982	Case report Preterm neonate, 28 weeks gestation, age 24 hours with total	Bolus: **100 mg/kg**	9.3 mg/kg	Bradycardia and 2:1 AV block resolved after initial bolus Calcium "returned to normal" after 5

	calcium 4.7 mg/dL post-transfusion	Infusion: **500 mg/kg/day**	46.5 mg/kg/day	days of infusion
Kurt 2006	Case report 10-day old infant with malignant infantile osteopetrosis and serum calcium 4.2 mg/dL	Bolus: **100 mg/kg** (Number of boluses unspecified)	9.3 mg/kg elemental	No calcium efficacy data Carpopedal spasm resolved
				(b) (4)

Corporate 2014	Drug Facts and Comparisons Textbook	Bolus: **200 mg** (maximum dose)	18.6 mg	No efficacy data
(b) (4)				

Synopses of Applicant's Pivotal Studies and Selected Other Publications:

Studies of Adult Patients:

Buchta, 2003 (*Transfusion*. 2003; 43: 1615-1621)

Title: *Reduction of Adverse Citrate Reactions during Autologous Large-Volume PBPC Apheresis by Continuous Infusion of Calcium Gluconate*

Design: Randomized, double blind, placebo control trial

Objectives: To assess the effect of continuous intravenous infusion of calcium gluconate during large volume leukapheresis in patients undergoing peripheral blood progenitor cell apheresis

Study Population:
50 male and female adult patients with hematologic or solid organ cancers
- Excluded: 1

Analyzed: 49
- Calcium gluconate: 24
- Placebo: 25

Inclusion and Exclusion Criteria
- Not specified

Withdrawal Criteria
- Investigators excluded one subject randomized to calcium who received placebo

Schedule and Duration:
The study consisted of an undefined screening period, and approximately three to five hours of apheresis. Subjects received the calcium gluconate infusion or placebo during apheresis. Investigators evaluated procedure-related discomfort, including symptoms of hypocalcemia, with a standardized questionnaire (1-6) and a visual analog scale (0-10)

Study Treatments:
Investigators randomly assigned subjects to one of two study arms.
- Calcium gluconate 4000 mg in 500 mL saline at 100 mL/hour
- Placebo infusion (saline 500 mL at 100 mL/hour)

Statistical Considerations:
The article did not specify a primary endpoint. Investigators compared post-treatment variables to baseline with *t*-test, U test, or Fisher's exact test.

Summary of Efficacy and Safety Findings:
Investigators analyzed 49 subjects, of who 24 received calcium gluconate. Median age was higher among subjects treated with calcium gluconate. Otherwise, demographics and baseline characteristics were similar between arms.

Table 2: *Demographics and Baseline Characteristics (Buchta 2003)*

	Placebo	**Calcium gluconate**
N	25	25
Age (years)	49 (17-66)	53 (20-69)
Male/Female	12/13	13/12
Citrate infused (mg/kg)	536.1 (429-697)	516.1 (428-677)
Apheresis time (minutes)	266 (210-301)	258 (237-303)
Values represent median and range		

The article did not report laboratory values, only percent changes from baseline. Serum ionized calcium decreased (-26.9 ± 10.4%) in the placebo arm compared to -10.4 ± 6.5% in the calcium gluconate arm ($p < 0.0001$). Total serum calcium decreased (-4.2%) in the placebo arm, and increased (+6.9%) in the calcium gluconate arm. Phosphorus decreased by a greater magnitude in the placebo arm. Changes in potassium and magnesium were similar between arms. Symptom scores were higher in the placebo arm. The article did not report precise values, but reported these results in bar charts. The mean scores on the ordinal scale (1-6) were approximately 2.7 for placebo compared to about 1.6 for calcium gluconate. The mean scores on the visual analog scale (0-10) were approximately 3.5 for placebo compared to about 1.8 for calcium gluconate.

Reviewer comments:
Calcium gluconate mitigated the decrease in serum calcium associated with citrated blood. Because the article did not report serum calcium values, it is unclear to what extent the treatment prevented hypocalcemia.

(b) (4)

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Studies of Pediatric Patients:

Broner, 1984 (*J Pediatr*. 1990; 117: 986-989)

Title: *A Prospective, Randomized, Double-Blind Comparison of Calcium Chloride and Calcium Gluconate Therapies for Hypocalcemia in Critically Ill Children*

Design: Randomized, double blind, active control trial

Objectives: To compare the effect of a calcium chloride and calcium gluconate infusion on serum calcium concentration on pediatric patients with hypocalcemia

Study Population:
37 male and female pediatric intensive care unit patients with hypocalcemia

- Calcium gluconate: 20
- Calcium chloride: 17

Inclusion Criteria

- Age 1 day to 17 years
- Hypocalcemia (less than normal range, not specified)

Exclusion Criteria

- Calcium administration prior to ICU admission

Withdrawal Criteria

- No ionized calcium level after calcium therapy

Schedule and Duration:
The study consisted of an undefined screening period, a single dose of intravenous calcium, and a blood sample 30 minutes after the dose.

Study Treatments:
All subjects received a single dose of elemental calcium 0.136 mEq/kg (0.27 mg/kg):

- Calcium gluconate (29 mg/kg)
- Calcium chloride (10 mg/kg)

Statistical Considerations:
The article did not specify a primary endpoint. Investigators compared post-treatment variables to baseline with a paired Student's *t*-test, and change in ionized calcium between arms with an un-paired Student's *t*-test.

Summary of Efficacy and Safety Findings:
Investigators analyzed 37 subjects. Twenty subjects received calcium gluconate, and 17 subjects received calcium carbonate. The article did not report how many subjects investigators excluded in each arm due to missing data post-therapy. Subjects treated with calcium chloride had a higher mean age and underlying disease acuity rating.

Table 5: *Demographic and Baseline Characteristics (Broner 1984)*

	Calcium chloride	**Calcium gluconate**
N	17	20
Age (years)	3.7 ± 5.0	3.0 ± 4.7
Acuity rating (disease severity)	15.5 ± 3.7	13.2 ± 3.4
Mean arterial pressure (MAP)	66 ± 22	63 ± 17
Ionized calcium	1.03 ± 0.14	1.07 ± 0.12
Values represent mean and standard deviation		

Serum ionized calcium increased compared to baseline in both arms. Change in ionized calcium above baseline was 0.19 mmol/L (0.76 mg/dL) in the calcium chloride arm and 0.09 mmol/L (0.36 mg/dL) in the calcium gluconate arm ($p < 0.05$). Mean arterial pressure increased compared to baseline in the calcium chloride arm.

Reviewer comment:
Calcium gluconate 29 mg/kg increased serum ionized calcium 0.09 mmol/L (0.36 mg/dL) above baseline after 30 minutes in critically ill pediatric patients with hypocalcemia. The article reported greater change from baseline ionized calcium after calcium chloride. It is unclear if the treatment arms were similar at baseline or if withdrawals affected the reported results.

Helikson 1997 (*J Pediatr Surg*. 1997; 32: 1244-1246)

Title: *Hypocalcemia and Hyperphosphatemia after Phosphate Enema Use in a Child*

Summary: This was a case report of a three-year-old patient treated with phosphate enemas for constipation who presented with serum phosphorus 74.7 mg/dL (normal range: 2.5-4.0) and ionized calcium 0.22 mEq/L (0.11 mmol/L [0.44 mg/dL]). The patient was treated initially with calcium gluconate 2000 mg over 10-15 minutes (approximately 140 mg/kg/day based on the median weight for age). Ionized calcium increased to 0.72 mEq/L (0.36 mmol/L or 1.44 mg/dL) and serum phosphorus decreased to 44.9 mg/dL after 4-6 hours.

Reviewer comment:
Calcium gluconate 140 mg/kg/day increased serum ionized calcium 1.44 mg/dL above baseline after 4-6 hours in a pediatric patient with hypocalcemia.

(b) (4)

Studies of Neonatal Patients:

(b) (4)

(b) (4)

Scott, 1984 (*J Pediatr*. 1984; 104: 747-751)

Title: *Effect of Calcium Therapy in the Sick Premature Infant with Early Neonatal Hypocalcemia*

Design: Partly randomized, open-label, three-arm, no-treatment control trial

Objectives: To evaluate the effect of a calcium gluconate bolus or infusion on serum calcium concentration in preterm neonates with hypocalcemia

Study Population:
27 male and female infants in a neonatal intensive care setting with hypocalcemia

- Calcium gluconate bolus: 9
- Calcium gluconate infusion: 9

- Control: 9

Inclusion Criteria

- Age less than 24 hours
- Ventilator therapy for respiratory distress syndrome
- Total serum calcium 6.0 mg/dL (1.50 mmol/L) or less

Exclusion Criteria

- Not specified

Schedule and Duration:
The study consisted of an undefined screening period, a 24-hour treatment period, and a 48-hour observation period following treatment.

Study Treatments:
Investigators randomly assigned subjects with ionized calcium $\geq$ 2.5 mg/dL (0.63 mmol/L) to one of three study arms, and subjects with ionized calcium < 2.5 mg/dL to one of the two active treatment arms (bolus or infusion).

- Calcium gluconate 200 mg/kg (100 mg/min) every 6 hours
- Calcium gluconate 400 mg/kg/day infusion
- No treatment

Statistical Considerations:
The article did not specify a primary endpoint. The article did not describe the statistical methods or a sample size calculation.

Summary of Efficacy and Safety Findings:
Investigators enrolled nine subjects in each arm, all of whom completed the study. Baseline demographic characteristics were similar between the active treatment arms. Mean gestational age and Apgar scores were higher in the control arm compared to the active treatment arm. The article did not report precise serum calcium levels, but instead presented all calcium data in figures. Ionized serum calcium values were approximately 3.0 mg/dL in the placebo and bolus arms and 3.1 mg/dL in the infusion arm at baseline, and approximately 3.5 mg/dL in all three arms at both 6 and 12 hours. At 24 hours, ionized serum calcium was approximately 3.6 mg/dL in the placebo arm, 3.8 mg/dL in the bolus arm, and 3.4 mg/dL in the infusion arm. Investigators reported statistically significant increases in both ionized and total serum calcium in all three arms at 24 hours compared to baseline ($p < 0.01$).

> *Reviewer comment:*
> *Calcium gluconate increased serum ionized calcium above baseline after 24 hours in neonatal patients with hypocalcemia. Intermittent bolus doses totaling 800 mg/kg/day increased ionized calcium by 0.72 mg/dL, and continuous infusion of 400 mg/kg/day increased ionized calcium by 0.3 mg/dL.*

Venkataraman 1985b (*Am J Dis Child*. 1985; 139: 913-916)

Title: *Postnatal Changes in Calcium-Regulating Hormones in Very-Low-Birth-Weight Infants*

Summary: This was a single arm study involving eight pre-term neonates, born at less than 32 weeks gestational age, presenting with serum calcium less than 6.0 mg/dL. The mean weight was 1027 grams, and mean gestational age was 28.4 weeks. Subjects received 18 mg/kg of elemental calcium as calcium gluconate (200 mg/kg) administered over 10 minutes. Total serum calcium increased about 4 mg/dL acutely and 1.9 mg/dL at eight hours. The ionized calcium level increased about 2.9 mg/dL acutely and 0.4 mg/dL at eight hours.

Table 7: *Serum Calcium Before and After Calcium Infusion (Venkataraman 1985b)*

	Total calcium (mg/dL)	**Ionized calcium (mg/dL)**
Baseline	7.9 ± 0.6	4.82 ± 0.24
Nadir	5.2 ± 0.2	3.72 ± 0.19
Peak	9.17 ± 0.74	6.68 ± 0.32
8-hours post	7.1 ± 0.5	4.12 ± 0.21

Reviewer comment:
Calcium gluconate 200 mg/kg increased serum ionized calcium 0.4 mg/dL after eight hours in preterm neonates with hypocalcemia.

Brown 1982 (*J Pediatr*. 1982; 100: 777-781)

Title: *Short-term Biochemical Effect of Parenteral Calcium Treatment of Early-Onset Neonatal Hypocalcemia*

Summary: This was a single arm study involving 24 neonates in intensive care with total serum calcium less than 7.0 mg/dL. The mean gestational age was 31 weeks, and mean weight was 1.58 kg. Subjects received calcium gluconate 200 mg/kg, infused over two minutes. Investigators obtained blood samples at 5, 20, 90, and 300 minutes. Total serum calcium increased 4.6 mg/dL above baseline at five minutes and 0.9 mg/dL at 300 minutes. Ionized calcium increased 2.0 mg/dL at five minutes and 0.4 mg/dL at 300 minutes.

Table 8: *Serum Calcium Before and After Calcium Infusion (Brown 1982)*

	Total (mg/dL)	Ionized (mg/dL)
Baseline	6.66 ± 0.12	3.03 ± 0.09
5 minutes	11.27 ± 0.22	5.00 ± 0.13
20 minutes	10.05 ± 0.20	4.41 ± 0.13
90 minutes	8.52 ± 0.15	3.88 ± 0.07
300 minutes	7.54 ± 0.13	3.40 ± 0.09

Reviewer comment:
Calcium gluconate 200 mg/kg increased serum ionized calcium 0.4 mg/dL above baseline after five hours.

Bifano 1989 (*Pediatr Res*. 1989; 25: 262-265)

Title: *The Cardiopulmonary Effects of Calcium Infusion in Infants with Persistent Pulmonary Hypertension of the Newborn*

Summary: This was a randomized crossover study that evaluated 10 neonates with persistent pulmonary hypertension of the newborn (PPHN). Included subjects were less than 72 hours old, born at 37 weeks gestational age or greater, with ionized calcium less than or equal to 3 mg/dL. Subjects received a single dose of calcium gluconate 200 mg/kg (administered over 2 minutes) or a saline infusion, with a 70 minute washout period between treatments.

Table 9: *Serum Calcium Before and After Calcium Infusion (Bifano 1989)*

Time (minutes)	Total calcium (mg/dL)	Ionized calcium (mg/dL)
-10	7.1 ± 0.3	2.6 ± 0.1
5	13.8 ± 0.4	6.1 ± 0.3
15	11.4 ± 0.5	5.1 ± 0.3
35	9.7 ± 0.4	4.2 ± 0.3
55	9.2 ± 0.5	3.7 ± 0.2

The article also reported improved echo parameters (right and left ventricular systolic time intervals) and improved oxygenation following calcium infusion.

Reviewer comment:
Calcium gluconate 200 mg/kg increased serum ionized calcium 1.1 mg/dL above baseline after 55 minutes.

Summary of Efficacy Findings:

Table 10 summarizes treatment doses and changes in serum ionized calcium levels in randomized, controlled trials and selected non-randomized studies and case reports. The effect of intravenous calcium gluconate on serum ionized calcium is consistent across diverse populations.

In adults with hypocalcemia, cumulative doses of calcium gluconate 1000 mg/day increased serum ionized calcium approximately 0.2-0.4 mg/dL (0.05-0.10 mmol/L), 2000 mg/day increased serum ionized calcium 0.4-0.6 mg/dL (0.10-0.15 mmol/L), and 4000 mg/day increased serum ionized calcium approximately 1.0 mg/dL (0.25 mmol/L) after one day.

In pediatric patients greater than one month of age, the paucity of data limits the conclusions somewhat. In one randomized trial, patients treated with a single dose of calcium gluconate 29 mg/kg experienced an increase in ionized calcium of 0.37 mg/dL (0.09 mmol/L) above baseline after 30 minutes. Case studies reported that infusions of calcium gluconate 150-250 mg/kg/day increased ionized calcium in individual patients approximately 1.0-1.5 mg/dL (0.25-0.38 mmol/L) after 6-72 hours. Infusions of 300 mg/kg/day increased total serum calcium approximately 3.6-4.0 mg/dL (0.9-1.0 mmol/L) after 1-9 days. The findings are consistent, as ionized calcium represents about 50% of total serum calcium.

In randomized trials of neonates, bolus doses of calcium gluconate 100-200 mg/kg increased serum ionized calcium by up to 1.0 mg/dL (0.25 mmol/L) acutely (2 minutes), and 0.4-0.5 mg/dL (0.10-0.12 mmol/L) over 1-8 hours. Continuous infusion or repeated boluses providing 400-800 mg/kg/day of calcium gluconate increased ionized calcium approximately 0.3-0.7 mg/dL (0.08-0.18 mmol/L) over 24 hours.

Table 10: Increase in Serum Ionized Calcium by Dose and Age Group

Source	Subjects	Total Daily Dose: Calcium gluconate	Infusion time	Ionized Calcium Increase (mg/dL)	Time of assessment
Adult Patients					
[redacted] (b) (4)					

Pediatric Patients Ages (> 1 month to < 17 years)					
Broner 1984	20	29 mg/kg	Bolus–NS	0.37	30 minutes
(b) (4)					
Helikson 1997	1	111 mg/kg	20-30 minutes	1.0	6 hours
(b) (4)					

Neonatal Patients (< 1 month)					
(b) (4)					
Bifano 1989	10	200 mg/kg	2 minutes	1.1	1 hour
Venkat. 1985b	8	200 mg/kg	10 minutes	0.4	8 hours
Brown 1982	24	200 mg/kg	2 minutes	0.4	5 hours
Scott 1984	9	400 mg/kg	24 hours	0.3	24 hours
(b) (4)					
Scott 1984	9	800 mg/kg	24 hours	0.72	24 hours

Summary of Dosing:

Table 11 summarizes dosing and administration reported in clinical studies, review articles, expert guidelines, and textbooks.

Dosing of calcium salts in published literature may be confusing due to inconsistent terminology and units of measure. In the articles reviewed, some authors reported the dose of calcium gluconate as milligrams (mg) of calcium gluconate or milliliters (mL) of calcium gluconate 10%. Others reported dosing in terms of mg, millimoles (mmol), or milliequivalents (mEq) of *elemental calcium* delivered by the product. Most pediatric articles reported doses adjusted per kilogram (kg) of body weight. Some publications reported continuous infusion rates in adult patients in mg/kg per hour (or minute) of elemental calcium. Standard dosing in the product label will reflect the dose (in mg) of the drug product (calcium gluconate), and provide conversions where appropriate.

Calcium Gluconate Injection contains 100 mg/mL of calcium gluconate. The concentration of calcium gluconate in the drug product is identical to that of marketed, unapproved products known as Calcium Gluconate Injection, USP 10%. One mL of the Calcium Gluconate Injection contains 9.3 mg of elemental calcium, equal to 0.465 mEq or 0.2325 mmol of elemental calcium. Alternatively, 1 mg of *elemental calcium* (0.25 mmol, or 0.5 mEq) converts to 10.75 mg of calcium gluconate (approximately 0.11 mL of Calcium Gluconate Injection).

Table 11: Dosing Reported in Published Literature

Bolus doses in adult patients					
Reference	**Subjects**	**Dose**	**Dilution**	**Time**	**Rate**
(b) (4)					
AHA 2005 *Guideline*	N/A	1000-2000 mg	NS	10 min	100-200 mg/min
(b) (4)					

Continuous infusions in adult patients					
Reference	**Subjects**	**Dose**	**Dilution**	**Time**	**Rate**
(b) (4)					
AHA 2005 *Guideline*	N/A	6600-16500 mg	6-8 mg/mL	6-12 hours	5.4-21.5 mg/kg/hr 324-2150 mg/hr
(b) (4)					

(b) (4)

Bolus doses in pediatric patients (>1 month to <17 years)					
Reference	**Subjects**	**Dose**	**Dilution**	**Time**	**Rate**
Broner 1984	20	29 mg/kg	NS	NS	NS
Helikson 1997	1	55 mg/kg (x 2)	NS	10-15 min	5 mg/kg/min 100 mg/min

(b) (4)

AAP 1998	N/A	60 mg/kg	NS	NS	NS

(b) (4)

Continuous infusions in pediatric patients (> 1 month to < 17 years)					
Reference	**Subjects**	**Dose**	**Dilution**	**Time**	**Rate**

(b) (4)

(b) (4)

Bolus doses in neonatal patients (≤ 1 month)					
(b) (4)					
Fishbein 1982	1	100 mg/kg	NS	NS	NS
Kurt 2006	1	100 mg/kg	NS	NS	NS
(b) (4)					
Scott 1984	9	200 mg/kg Every 6 hours	NS	NS	100 mg/min
Bifano 1989	10	200 mg/kg	NS	2 minutes	100 mg/kg/min
Mirro 1984	16	200 mg/kg	NS	2 minutes	100 mg/kg/min
Venkataraman 1985b	8	200 mg/kg	50 mg/mL	10 minutes	20 mg/kg/min
Brown 1982	24	200 mg/kg	NS	2 minutes	100 mg/kg/min
Salsburey 1982	24	200 mg/kg	NS	NS	100 mg/min
(b) (4)					
Corporate 2014 *Textbook*	N/A	200 mg	NS	NS	NS

(b) (4)

Continuous infusions in neonatal patients (≤ 1 month)

Reference	Subjects	Dose	Dilution	Time	Rate
(b) (4)					
Scott 1984	9	400 mg/kg	NS	24 hours	17 mg/kg/hour
(b) (4)					
Fishbein 1982	1	500 mg/kg	NS	24 hours	21 mg/kg/hour
(b) (4)					

The Applicant proposes an initial bolus dose in adult patients of 1000 to 2000 mg, administered (b) (4) One clinical trial ((b) (4)), three non-randomized studies ((b) (4), (b) (4), (b) (4)), review articles ((b) (4), (b) (4), (b) (4)), and guidelines ((b) (4), (b) (4)) support the proposed dose. One review article (b) (4)

Recommended infusion rates in reviews and guidelines vary considerably. The Applicant proposes a continuous infusion dose of (b) (4) mg/day, based on (b) (4) This dose, however, represents only the recommended dilution ((b) (4)). (b) (4)

(b) (4)
(b) (4)
recommends a similar regimen.
(b) (4)

In pediatric patients, > 1 month to < 17 years, the Applicant proposes a single bolus dose of [redacted]. The Applicant derived the bolus dose from the [redacted]. One clinical trial in this population (Broner, 1984), reported a single bolus dose of 29 mg/kg, and case reports in the literature reported bolus doses from 55 mg/kg up to 90 mg/kg (*Helikson, 1997,* [redacted]). Guidelines support boluses up to 60 mg/kg (*American Academy of Pediatrics, 1998*). The literature does not clearly support the repeat doses [redacted].

The Applicant proposes a continuous infusion rate of [redacted] mg/kg/day in pediatric patients > 1 month to < 17 years. Most case reports in pediatric patients support continuous infusion doses up to 300 mg/kg/day. Reviews and textbooks recommend continuous infusion up to 800 mg/kg/day, but the upper end of this range appears to be derived from studies in neonates, and may not be applicable to the entire age group.

In neonatal patients ≤ 1 month, the Applicant proposes bolus doses of 100 to 200 mg/kg over [redacted] minutes, and repeat doses every six hours. The literature, including randomized trials, supports the doses ([redacted], *Scott, 1984, Bifano, 1989, Mirro, 1984, Venkataramen, 1985b, Brown, 1982, Salsburey, 1982*). Reviews generally recommend infusion over [redacted].

The Applicant proposes a continuous infusion rate of [redacted] in neonatal patients. Randomized trials support [redacted], *Scott, 1984*). Review articles and textbooks support [redacted].

In summary, the literature supports the following dosing, summarized in Table 12.

Table 12: Summary of Dosing Recommendations

		Follow-up Dose	
Patients	**Initial Bolus Dose**	**Repeat Bolus**	**Continuous Infusion**
Adult patients	1000-2000 mg [redacted]	1000-2000 mg every 6 hours	5.4-21.5 mg/kg/hour
Pediatric patients ages > 1 month to < 17 years	29-60 mg/kg	29-60 mg/kg every 6 hours	8-13 mg/kg/hour [redacted]
Neonatal patients ages ≤ 1 month	100-200 mg/kg	100-200 mg/kg every 6 hours	17-33 mg/kg/hour [redacted]

The literature supports the following additional recommendations related to administration and monitoring of serum calcium:

- (b) (4)
- (b) (4)
- The infusion rate should not exceed 200 mg/minute is adults or 100 mg/minute in pediatric patients
- (b) (4)

Reviewer comment:
The literature supports the doses summarized in Table 12.

6.1.10 Additional Efficacy Issues/Analyses

The use of intravenous calcium salts, including calcium gluconate, predates the availability of reliable or prompt serum calcium assays.[8,9] Clinical studies reporting that calcium gluconate increased serum calcium levels were first published the early 1950s..[10,11] Currently, calcium gluconate is the most widely used calcium salt to treat acute symptomatic hypocalcemia. Calcium chloride is more likely to cause local irritation, especially when administered via peripheral veins.

It is not feasible or ethical to attempt to conduct adequate and well-controlled studies in the proposed patient population. All causes of acute hypocalcemia are rare, and critically ill patients with acute, symptomatic hypocalcemia represent a very heterogeneous population. A placebo control trial is probably unethical because the population is at high risk for serious complications without treatment. Comparison with approved therapy is unlikely to demonstrate substantial evidence of effectiveness, because 10% Calcium Chloride Injection, USP obtained approval via the 505(b)(2) pathway relying on the medical literature, without adequate and well-controlled studies.

8 Lloyd. Br Med J 1928; 1(3511): 662-664
9 McCance. Biochem J 1939; 33(4): 523-529
10 Howard. J Clin Endocrinol Metab 1953; 13(1): 1-19
11 Goldman. J Clin Endocrinol Metab 1954; 14(3): 278-86

The FDA guidance “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” (May 1998) includes a list of factors that increase the possibility of reliance on published reports alone to support approval of a new product or new use:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.
b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.
d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).
e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

Reviewer comment:
The application does not meet the standards for study design, data collection, or analyses outlined in the guidance, but factors specific to this product mitigate these defects. Measurement of serum ionized calcium before and after infusion of calcium gluconate is a face-valid clinical outcome. Clinical symptoms and signs are closely associated with serum ionized calcium levels, although the threshold varies individually depending on the magnitude and acuity of onset of hypocalcemia. The clinical studies submitted fulfill the purpose of investigations: “to distinguish the effect of the drug, calcium gluconate, from other influences such as spontaneous change in the course of the disease, placebo effect, or biased observation” as defined in 21CFR §314.126(a). Clinical laboratory measurement in the reported settings was not subject to these influences. Finally, the application fulfills the first standard, in that multiple studies, in different patient population demonstrate consistent results. That is, calcium gluconate rapidly increases serum ionized calcium and symptoms of hypocalcemia in patients with acute, symptomatic hypocalcemia.

7 Review of Safety

Safety Summary

The Applicant submitted information about adverse reactions from the published literature in support of safety. The articles did not report systematic, prospective collection or categorization of adverse events or other safety data. It is not possible to estimate the frequency of adverse reactions from the submitted data.

The Applicant submitted no case reports of death following or attributable to intravenous calcium gluconate. 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. Review articles, guidelines, and textbooks recommend infusing calcium gluconate slowly to avoid these complications.

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. Review articles, clinical practice guidelines, and textbooks recommend dilution of calcium gluconate prior to administration to decrease the risk of skin and soft tissue reactions.

Patients with acute, symptomatic hypocalcemia are at risk of serious complications and death. The Applicant did not submit data to support the use of Calcium Gluconate Injection for other indications. Appropriate patient selection, limiting the approved indication to acute, symptomatic hypocalcemia, will mitigate the risk of potential adverse reactions.

7.1 Methods

This review considered all article submitted by the Applicant in support of safety. The review omits articles reporting on the use of calcium gluconate for indications other than hypocalcemia that did not contain any relevant safety information. This review omits sections of the standard clinical review template that are not relevant to the Applicant's submission.

7.2 Adequacy of Safety Assessments

The Applicant submitted information about adverse reactions from the published literature used in support of this application. In general, the articles did not report systematic, prospective adverse events collection or pre-defined categorization of the severity of adverse events. Similarly, the articles did not report systematic collection of other safety assessments such as vital signs, physical examination, clinical laboratory data, imaging, and ECG. Ad hoc collection of adverse events or other safety findings most likely resulted in undercounting. Estimates of the frequency of adverse events are therefore not reliable.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Applicant submitted data from 150 articles reporting parenteral administration of calcium gluconate to 3298 subjects, including 2732 adults, 91 pediatric patients (ages one month to 17 years), and 347 neonatal patients. Among these, the Applicant included studies that reported on the use of parenteral calcium gluconate for other indications, in which the patients did not have hypocalcemia. This review excludes most of those articles, which are not relevant to the current application, unless the article contained relevant safety information pertinent to this application.

The articles reported bolus doses in adult patients mostly in the range of 1000-2000 mg, and cumulative doses (from repeated boluses or infusions) in adults up to (b) (4) per day. The vast majority of subjects received 4000 mg per day or less. In pediatric patients (greater than one month to less than 17 years), reported bolus doses ranged from 29 mg/kg to (b) (4). Articles reported cumulative dosed up to (b) (4). In neonatal patients, bolus doses ranged from 100 mg/kg to 200 mg/kg, and cumulative doses up to 800 mg/kg/day.

The submitted articles do not include special safety studies, such as explorations for dose response, metabolism, clearance, or drug interactions. The Applicant did not conduct any new studies in support of the application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

10% Calcium Chloride Injection, USP (NDA 021117) is approved for the treatment of hypocalcemia in “conditions requiring a prompt increase in plasma calcium levels.” The Applicant for NDA 021117 obtained approval by the 505(b)(2) pathway, relying entirely on the published literature for approval. As with the current application, the Applicant did not conduct new clinical studies to systematically assess the frequency and severity of adverse reactions with the use of intravenous calcium chloride. Adverse reactions listed

in the prescribing information include necrosis and sloughing associated with direct injection into perivascular tissues, potential for aluminum toxicity with prolonged administration, peripheral vasodilation, decreased blood pressure, and burning sensation associated with peripheral infusion. An older calcium chloride product (Abboject), originally marketed prior to 1938, did not require FDA approval for safety or efficacy.

7.3 Major Safety Results

Table 13 summarizes literature submitted in support of safety. The table includes 78 studies involving approximately 1478 patients with hypocalcemia treated with calcium gluconate and patients treated with calcium gluconate for other indications who experienced adverse reactions, including 1083 adults, 91 pediatric patients, and 304 neonatal patients. The table excludes submitted studies of patients treated for other indications that reported no adverse reactions.

Table 13: Studies to Support Safety

Studies of Adult Patients

Source	Population	Subjects	Dose: Calcium Gluconate	Safety Results
Celbek 2013	Hyperkalemia, porphyria	1	1000 mg	Extravasation Bullous skin lesions
Chen 2009	Gout, CKD	1	1000 mg	Upper extremity deep venous thrombosis
Dickerson 2005	Critical illness	37	1000-4000 mg/day	Hypercalcemia
Kagen 2000	Lymphoma	2	3000 mg/Not reported	Calcinosis cutis
Goertz 1994	CABG	9	15 mg/kg	Increased MAP, SVR, and LVSWI
Carlon 1978	Critical illness	1	20 mg/kg over 1 minute	Cardiac arrhythmias AV block
Russo 2014	Healthy volunteer	1	21.5 mg/kg @ 1000 mg/min	Cardiac arrest Asystole
Cheng 2012	Hypocalcemia Severe CP/MR	1	2000 mg every 6 hours 100 mg/kg (19.7 kg)	Vascular calcification Calcinosis cutis
Studies with no reported adverse events				
Kishimoto 2002	PBPC Apheresis	23	425-1500 mg/day	
Flagge 2011	SVT	1	1000 mg	
Steele 2013	Critical illness	539	1000 mg/day	
Martin 1990	Liver transplant	7	1800-3000 mg	
Dickerson 2007a	Critical illness	25	2000-4000 mg/day	
Buchta 2003	Apheresis	25	3844 mg/day	
Dickerson 2007b	Critical illness	20	4000 mg/day	
Loke 2009	Parathyroidectomy	36	10800-21600 mg/day	
Nakagawa 2000	Parathyroidectomy	49	11000 mg/m2	
Kankirawatana 2007	Plasma exchange	84	216 mg/500 mL albumin	

Brunner-Spiering 2013	Apheresis	195	1000 mg/hour	
Levine 2011	Digoxin toxicity	23	Not reported	
Belluzzo 2011	Seizure	1	Not reported	
Whitson 2006	Bisphosphonate	1	Not reported	
Kostoglu-Asthanassiou 2015	Barakat syndrome Hypoparathyroidism	1	Not reported	

Studies of Pediatric Patients > 1 month to < 17 years

Source	Population	Subjects	Dose: Calcium Gluconate	Safety Results
Lakhani 1996	Hypocalcemia Convulsions	1	Not reported	Subcutaneous calcification
Raffaella 2009	Tumor lysis	1	200-300 mg/kg/day	Calcinosis cutis
Sivrioglu 2014	Neonatal: 3/9 > 1 month	3	Not reported	Extravasation Skin necrosis
Devlin 1990	Atopic eczema	2	40-400 mg/kg/day	Atopic eczema
Caksen 2002	Neonatal sepsis Acute renal failure	1	Not reported	Subcutaneous calcification
Moss 2006	Osteogenic sarcoma	1	Not reported	Calcinosis cutis
Orellana 2002	Fever, cellulitis	1	Not reported	Calcinosis cutis
Soon 2001	Critical illness	2	Not reported	Calcinosis cutis
Studies with no reported adverse events				
Cho 2013	Pseudo-hypoparathyroidism Cardiomyopathy	1	5-8 mg/kg/day	
Maltz 1970	Rickets	1	10 mg/kg	
Jaffe 1972	Leukemia	14	20-100 mg/kg	

Broner 1990	Critical illness	20	29 mg/kg	
Thakur 2008	Paromomycin	3	30-125 mg/kg	
Kossoff 2002	Vitamin D deficiency	1	75 mg/kg/day	
Hebbar 2006	Hyperphosphatemia	1	85 mg/kg	
Edmondson 1990	Hyperphosphatemia	1	90 mg/kg	
Helikson 1997	Hyperphosphatemia	1	140 mg/kg	
Geffner 1980	Hyperphosphatemia	1	300 mg/kg/day	
Morrell 1984	Cardio-pulmonary bypass	29	>1000 mg	
Latorre 1974	Osteomalacia	1	1600 mg/kg/day	
Gera 2012	Posterior reversible encephalopathy Hypocalcemia	1	2500 mg/day (180 mg/kg)	
Karademir 1993	Hypocalcemia, seizures	1	Not reported	
Kishimoto 2002	PBPC apheresis	3	Not specified	

Studies of Neonatal Patients (≤ 1 month)

Source	Population	Subjects	Dose: Calcium Gluconate	Safety Results
Locham 2002	Citrate Exchange transfusion	15	100 mg per 100 mL exchanged blood	Cardiac arrest (1 case)
Weiss 1975	Neonatal	4	54 mg/kg/hour 1:1 dilution	Skin necrosis (4/45)
Mu 1999	Neonatal	9	300-400 mg/kg/day No dilution	Calcinosis cutis (9/103)
Khan 2010	Prophylactic IV calcium	40	400 mg/kg/day Dilution not specified	Local tissue necrosis (14/40 normal calcium, 4/22 with hypocalcemia)
Roberts 1977	Neonatal	4	62-195 mg/kg	Calcinosis cutis
Hironaga 1982	Premature Normal calcium	1	170 mg/kg	Calcinosis cutis Skin necrosis
Domizio 2006	Meningitis, seizure	1	200 mg/kg/day	Calcinosis cutis

Ergin 2011	Pseudo-hypoparathyroidism	1	200-400 mg/kg/day	Calcinosis cutis
Ramamurthy 1975	Neonatal	9	200-800 mg/kg/day	Calcinosis cutis
Sonohata 2008	Neonatal	1	255 mg (90 mg/kg)	Calcinosis cutis Extravasation
Berger 1974	Neonatal	3	400-500 mg (125-150 mg/kg) Not reported (2)	Subcutaneous calcification Skin necrosis
Puvabanditsin 2005	Neonatal	1	500 mg/kg/day x 14 days	Soft tissue calcification Skin necrosis
Cherian 2013	Neonatal	1	Not reported	Calcinosis cutis
Chen 2010b	Neonatal	1	Not reported	Calcinosis cutis Cellulitis
Packer 1984	Neonatal	1	Not reported	Soft tissue calcification
Chiang 2004	Neonatal	1	Not reported	Extravasation Cellulitis Osteomyelitis
Sivrioglu 2014	Neonatal: 6/9 < 1 month	6	Not reported	Extravasation Skin necrosis
Goldsmith 1981	Bronchopulmonary dysplasia	1	200-700 mg/kg/day x 6 weeks plus furosemide	Bilateral renal calculi Hypercalciuria
	Premature infants	13	320-473 mg/kg/day	Hypercalciuria
Brown 1982	Neonatal	24	200 mg/kg	Increased excretion of K, Mg, Ca Non-adverse
Mirro 1984	Neonatal	16	200 mg/kg	Increased BP and HR Non-adverse
Salsburey 1982	Neonatal	24	200 mg/kg	Increased BP and HR Non-adverse
Venkataraman 1991	Neonatal	36	18 mg/kg elemental	Decreased pH: 7.36 to 7.33

			200 mg/kg gluconate	Decreased phosphorus Non-adverse
Studies with no reported adverse events				
Kurt 2006	Neonatal	1	100 mg/kg	
Fishbein 1982	Neonatal	1	100 mg/kg	
Porcelli 1995	Neonatal	22	100 mg/kg	
Robertson 2002	Neonatal, with seizures	1	180-360 mg/kg	
Venkataraman 1985b	Neonatal	8	200 mg/kg	
Bifano 1989	PPHN	10	200 mg/kg	
Brown 1981	Neonatal	36	400-600 mg/kg/day	
Scott 1984	Neonatal	9	400-800 mg/kg/day	
Al-Wahab 2001	Neonatal	1	430 mg/kg/day	
Borkenhagen 2013	Neonatal	1	Not reported	

7.3.1 Deaths

The Applicant submitted no case reports of death following or attributable to intravenous calcium gluconate

7.3.2 Nonfatal Serious Adverse Events

The Applicant submitted data reporting on cardiac arrhythmia and cardiac arrest associated with rapid injection of calcium gluconate in patients.

Carlon, 1978 reported two cases of arrhythmia associated with rapid infusion of intravenous calcium. In the first case, a critically ill 67-year-old female patient with sepsis and ionized calcium 1.85 mEq/L (normal range: 1.8-2.2; equivalent to 3.7 mg/dL) developed atrioventricular dissociation, ST depression, and hypotension with junctional escape rhythm, immediately after receiving calcium chloride 7 mg/kg over one minute. Concomitant medications included digoxin. ECG abnormalities resolved over the next 20 minutes. In the second case, a 43-year old patient with gastrointestinal hemorrhage and ionized calcium 1.68 mEq/L (3.4 mg/dL) received calcium gluconate 20 mg/kg intravenously over one minute and developed junctional tachycardia and hypotension, which resolved after about 15 minutes.

Russo, 2014 reported the case of a 28-year-old healthy male volunteer, who received calcium gluconate 2 mg/kg at a rate of 10 mL/min (1000 mg/min) in a study to evaluate reference levels for a calcium stimulation test. The subject became unresponsive, and ECG revealed asystole, which resolved during cardiopulmonary resuscitation. The article referenced two previous cases of atrial fibrillation following calcium stimulation tests at the same dose.

Locham, 2002 reported one case of cardiac arrest in a neonate with neonatal jaundice undergoing exchange transfusion. Patients in the study received 100 mg calcium gluconate per 100 mL of blood exchanged. The article provided no additional details.

No clinical trials evaluated strategies to decrease the risk of cardiac arrhythmias or cardiac arrest. Review articles, clinical practice guidelines, and textbooks recommend infusing calcium gluconate slowly, no more than 200 mg/minute in adults, and no more than (b) (4) in children and neonates ((b) (4))

Intravenous administration of calcium gluconate may result in calcinosis cutis, with associated tissue necrosis, ulceration, and secondary infection. Refer to Section 7.4.1—*Common Adverse Events* of this review for details.

Reviewer comment:
Rapid injection of calcium gluconate may cause bradycardia, decreased blood pressure, cardiac arrhythmias (including atrial fibrillation, atrioventricular block, and asystole), and cardiac arrest.

7.3.3 Dropouts and/or Discontinuations

Several of the articles from the published literature, including articles reporting randomized trials, reported dropouts or discontinuations. In some cases, the authors did not report reasons for withdrawal. The articles generally did not report data collection after withdrawals.

7.3.4 Significant Adverse Events

Venous thrombosis:
Chen, 2009 reported a case of a 61-year old man with a history of gouty nephropathy requiring hemodialysis, who developed upper extremity deep venous thrombosis shortly after infusion of calcium gluconate 1000 mg into the same arm.

Vascular calcification:
Cheng 2012 reported a case of calcinosis cutis and vascular calcification following intravenous calcium gluconate in a 19-year old with cerebral palsy and mental retardation.

Refer to Section 7.3.2—*Nonfatal Serious Adverse Events* for discussion of cardiac adverse reactions related to rapid infusion of calcium gluconate and Section 7.4.1—*Common Adverse Events* for discussion of calcinosis cutis due to calcium gluconate infusion and complications of extravasation of calcium gluconate.

Reviewer comment:
The temporal associations implicate venous thrombosis and vascular calcification as possible adverse reactions associated with intravenous calcium.

7.3.5 Submission Specific Primary Safety Concerns

Flushing:
Morimoto, 1979 reported transient flushing sensation in healthy volunteers administered calcium gluconate 4 mg/kg over one minute. *Graudins, 1997* reported local warmth, burning, and discomfort in patients with hydrofluoric acid burns treated with intravenous infusion distal to a tourniquet or intra-arterial infusion of calcium gluconate. The Applicant did not submit data related to these effects in patients with acute, symptomatic hypocalcemia.

Reviewer comment:
The submission does not support the inclusion in the label of "flushing" as an adverse reaction associated with calcium gluconate for the treatment of acute, symptomatic hypocalcemia.

Atopic eczema:
The applicant submitted a case series (*Devlin, 1990*) of two pediatric patients (ages 3 years 7 months, and 8 years 6 months) with a history of atopic eczema and multiple food allergies, each of whom experienced exacerbation of eczema temporally related to calcium gluconate infusion, but confounded by other foods, medications, and oral calcium supplements. The first patient experienced pruritus and worsening rash 3-4 days after infusion, and the second experienced transient pruritus and erythema two hours after infusion.

Reviewer comment:
Multiple confounders limit attribution of exacerbation of atopic eczema to intravenous calcium gluconate.

Renal calculi:
Goldsmith, 1981 reported a case of renal calculi in an eight-week-old infant with bronchopulmonary dysplasia treated with calcium gluconate 200 to 700 mg/kg/day for six weeks with concomitant furosemide.

Reviewer comment:
The case, involving long-term intravenous calcium infusion with concomitant furosemide, is not clearly applicable to treatment of acute, symptomatic hypocalcemia.

Increased parathyroid gland sensitivity:
The Applicant submitted data from two articles describing reactions or laboratory changes following calcium gluconate infusion under the category of "increased parathyroid gland sensitivity." *Ahmad, 2004* reported on a change in parathyroid responsiveness secondary to growth hormone (GH) replacement in patients with adult growth hormone deficiency, in which investigators assessed parathyroid hormone (PTH) levels in response to calcium infusion. The reported change in parathyroid function was secondary to GH, and unrelated to calcium gluconate itself. *Virtanen, 1998* reported a case of iatrogenic hypercalcemia resulting in decreased PTH levels and worsening left ventricular diastolic dysfunction. In this case, the decreased PTH level was physiologic, and non-adverse.

Reviewer comment:
The submission does not support the inclusion in the label of "increased parathyroid gland sensitivity" as an adverse reaction related to calcium gluconate for treatment of acute symptomatic hypocalcemia.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse reactions associated with intravenous calcium gluconate administration are skin and soft tissue conditions. Events reported in the literature include soft tissue inflammation, skin necrosis, and calcinosis cutis (or subcutaneous calcification). Authors of the publications did not report systematic grading of adverse event severity.

Iatrogenic calcinosis cutis secondary presents three days (*Ramamurthy, 1975*) to three weeks (*Roberts, 1977, Mu, 1999*) after the initial dose of intravenous calcium. Clinical findings include erythema, edema, papules, plaques, subcutaneous nodules, and skin sloughing (*Mu, 1999, Moss, 2006*). Radiologic findings include amorphous masses, plaques, or linear infiltration along perivascular tracts. Resolution occurs over three weeks to three months, and may result in residual cosmetic changes (*Mu, 1999*).

Skin and soft tissue reactions occur in all age groups (*Kagen, 2000, Cheng 2012, Caksen, 2002, Moss, 2006, Raffaella, 2009*), but most reports documented reactions in neonates (*Mu, 1999, Khan, 2010, Berger, 1974, Cherian, 2013, Chiang, 2004, Domizio, 2006, Ergin, 2011, Hironaga, 1982, Orellana, 2002, Packer, 1984, Puvabanditsin, 2005, Roberts, 1977, Ramamurthy, 1975, Siviroglu, 2014, Sonohata, 2008*).

In some reports, calcinosis cutis followed known extravasation of calcium gluconate infusions (*Khan 2010, Moss, 2006, Raffaella, 2009, Berger, 1974, Siviroglu, 2014, Hironaga, 1982*), but in other cases there was no documented history of extravasation (*Weiss, 1975, Domizio, 2006, Packer, 1974*). In two case reports, calcinosis occurred at a site distant from the infusion (*Soon, 2001, Puvabanditsin, 2005*). Complications of calcinosis include skin necrosis (*Khan, 2010, Weiss, 1975, Berger, 1974, Raffaella, 2009, Siviroglu, 2014*), secondary infection, and possibly osteomyelitis (*Chiang, 2004*). *Celbek, 2013* reported bullous skin lesions following calcium gluconate infusion for hyperkalemia in an adult patient.

Three articles attempted to estimates of frequency of soft tissue complications in neonates. *Mu, 1999* reported 9 cases of calcinosis among 103 consecutive neonates (8.7%) with hypocalcemia treated with calcium gluconate 300-400 mg/kg/day. *Khan, 2010* reported that 4 of 22 hypocalcemic patients (18%) who received intravenous

calcium 400 mg/kg/day developed skin necrosis. Neither article reported dilution of calcium gluconate. *Weiss, 1975* reported that 4 of 45 neonates (8.9%) treated with intravenous calcium gluconate 100 mg/mL diluted 1:1 in dextrose and water, and administered via a scalp vein developed localized skin necrosis.

No clinical trials evaluated strategies to decrease the risk of calcinosis cutis. Review articles, clinical practice guidelines, and textbooks recommend dilution of calcium gluconate 10 mg/mL with 5% dextrose or normal saline prior to administration (*Cooper, 2008, Society for Endocrinology, 2016*).

> *Reviewer comment:*
> *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 reports involved neonates. It is unclear if the reaction is more common in this population due to the relatively higher doses typically used to treat hypocalcemia or other factors. Skin necrosis is the most commonly reported complication of calcinosis cutis. Calcinosis and its complications typically resolve with supportive care. Calcinosis cutis may occur in the absence of gross extravasation, most likely as a result of local elevation of calcium levels in the presence of substrates, such as phosphate. Review articles, guidelines, and textbooks recommend dilution of calcium gluconate prior to administration.*

7.4.2 Laboratory Findings

The Applicant submitted several articles reporting laboratory changes, not all of which were adverse.

Decreased blood pH:
Venkataraman, 1991 reported decreased pH in 36 premature infants with hypocalcemia treated with intravenous calcium gluconate 200 mg/kg infused over 10 minutes. Investigators obtained blood samples on patients receiving repeat therapy over three days, not necessarily after the initial infusion. As a result, some patients were not hypocalcemic at the time of blood collection. Mean ionized serum calcium increased from 4.7 mg/dL at baseline to 6.9 mg/dL after infusion (normal ranges not reported). Blood pH decreased from a mean 7.36 at baseline to 7.33 after infusion in patients 2500 grams or less, and from 7.39 to 7.36 in patients greater than 2500 grams.

> *Reviewer comment:*
> *Mean serum ionized increased from the normal range to the hypercalcemic range. It is unclear if the small change in serum pH was clinically significant or adverse in these subjects, or how the serum ionized calcium and pH changed over the next several hours.*

Dickerson, 2007a reported no significant change in blood pH in 15 adult patients with mild hypocalcemia (serum ionized calcium 1.00-1.12 mmol/L, normal range not specified) six to eight hours after treatment with calcium gluconate 2000 mg over two hours. The article reported a significant *increase* in blood pH to the normal range (mean pH 7.41) in 10 adult patients with moderate to severe hypocalcemia (serum ionized calcium < 1 mmol/L) treated with calcium gluconate 4000 mg over four hours.

> *Reviewer comment:*
> *The article reported no change or non-adverse changes in pH in adult patients with hypocalcemia treated with calcium gluconate. In summary, change in blood pH is not a clinically significant adverse reaction associated with treatment of hypocalcemia with calcium gluconate.*

Hypercalcemia:
Dickerson, 2005 reported transient, mild hypercalcemia (ionized calcium 1.34 mmol/L, normal range not specified) in a patient treated with calcium gluconate 4000 mg over four hours.

> *Reviewer comment:*
> *The transient, mild increase in serum ionized calcium (the typical upper limit of normal is about 1.30-1.35 mmol/L) is of unclear clinical significance.*

Increased urine excretion of potassium and magnesium:
Brown, 1982 reported increased urine excretion of serum electrolytes following intravenous calcium gluconate 200 mg/kg in 24 preterm neonates with hypocalcemia. Increases in excretion of potassium and magnesium were relative to baseline values, and not necessarily abnormal or adverse. Blood potassium and magnesium levels were unchanged.

> *Reviewer comment:*
> *The reported change in urine excretion of potassium and magnesium was not abnormal or adverse.*

Other laboratory changes:
The Applicant submitted reports of several other laboratory changes that were non-adverse. These laboratory changes represent physiologic responses to increases in ionized calcium in healthy subjects with normal baseline calcium levels treated with intravenous calcium gluconate. Three authors (*Giovanella, 2012, Herfarth, 1992*, and *Morimoto, 1979*) reported increased serum calcitonin level after calcium gluconate

infusion in healthy subjects. *Giudieri, 1994* reported increased plasma adenosine after calcium gluconate infusion in healthy subjects.

> *Reviewer comment:*
> *Increased serum calcitonin and increased plasma adenosine are physiologic, non-adverse reactions to increased ionized calcium in healthy subjects.*

7.4.3 Vital Signs

The applicant submitted several reports describing changes in vital signs associated with calcium gluconate infusion.

Increased blood pressure:
Two single arm studies of preterm neonates with hypocalcemia (*Mirro, 1984* and *Salsburey, 1982*) reported increased blood pressure associated with calcium gluconate infusion 200 mg/kg. In both articles, patients were critically ill, and the authors reported the changes in the context of improvement in systolic function. *Goertz, 1994* reported an increase in blood pressure and systemic vascular resistance in cardiac surgery patients following a bolus of calcium gluconate 15 mg/kg, but no change in heart rate, pulmonary pressures, or cardiac output or other parameters of cardiac function. *Hempelman, 1978* reported increased cardiac index in addition to increased blood pressure and systemic vascular resistance.

Suzuki, 1988 reported increased blood pressure in healthy adult volunteers with and without hypertension during calcium gluconate infusions of 3.75 to 15.0 mg/kg/hour. Subjects had normal calcium at baseline and elevated serum calcium during infusion.

> *Reviewer comment:*
> *Calcium gluconate may increase blood pressure—without causing hypertension—in certain clinical scenarios in patients with hypocalcemia. The data submitted indicates that the changes are non-adverse—either neutral or salutary on cardiac function. Continuous calcium infusion in normocalcemic adults that results in hypercalcemia may cause an adverse increase in blood pressure, but the effect is not relevant to treatment of acute, symptomatic hypocalcemia.*

Increased heart rate:
Mirro, 1984 and *Salsburey, 1982* also reported increased heart rate (6-8 beats per minute) in preterm neonates treated with intravenous calcium gluconate in the context of improvement in cardiac function. Studies in adults (*Goertz, 1994*) demonstrated no change in heart rate.

Reviewer comment:
Calcium gluconate may cause non-adverse increases in heart rate in some populations.

7.4.4 Electrocardiograms (ECGs)

The submitted articles in patients in patients with hypocalcemia did not report any significant ECG changes. When evaluated, there was no association between intravenous calcium gluconate infusion and QT interval changes (*Scott, 1984*).

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.5 Drug-Drug Interactions

Hypercalcemia increases the risk of digoxin toxicity. Co-administration of calcium and cardiac glycosides may cause synergistic arrhythmias.

Administration of calcium may reduce the response to calcium channel blockers.

Refer to the Clinical Pharmacology review for complete discussion of drug interactions. Refer to the Division of Pediatric and Maternal Health memorandum for discussion of neonatal fatalities related to concomitant use of ceftriaxone and calcium gluconate.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant did not submit any data related to carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

The Applicant did not submit any studies of the use of calcium gluconate during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

This review discusses safety data in neonatal patients and pediatric patients, ages greater than one month to less than 17 years, in Sections 7.1 through 7.5. Safety issues in pediatric patients are similar to those in adults. The most common adverse reactions are skin and soft tissue disorders (such as subcutaneous calcification), and the most serious adverse reactions are cardiac arrhythmias and cardiac arrest, associated with rapid infusion. Calcium is necessary for normal growth and development.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant submitted information regarding symptoms and signs of hypercalcemia. Rapid infusion of parenteral calcium may result in transient hypercalcemia. The clinical consequences could include myocardial depression, increased blood pressure, and atrioventricular block. Use of the product within the appropriate dosing range, and proper administration—including dilution and appropriate delivery rate—mitigate these effects in patients with hypocalcemia. Frequent assessment of serum calcium concentration, coupled with adjustment or discontinuation, mitigates the risk of hypercalcemia during parenteral infusion.

Chronic symptoms and signs of hypercalcemia, such as gastrointestinal symptoms, peptic ulcers, fluid and electrolyte losses by the kidney, and neurologic symptoms are not relevant to acute parenteral treatment of symptomatic hypocalcemia.

Calcium gluconate does not have abuse potential.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

The Applicant submitted data from a search of the FDA Adverse Event Reporting System (FAERS). The most common adverse events in the FAERS search included conditions that cause hypocalcemia, such as toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS). Other common adverse events included skin and soft tissue reactions associated with parenteral calcium infusion, such

as calcinosis, extravasation, and skin necrosis. Other events captured by the FAERS search included medication errors and product quality issues, such as bacterial contamination. The Applicant did not provide patient narratives that would further inform the search data.

Reviewer comment:
The FAERS search did not provide any additional safety information to inform the benefit-risk evaluation of the product.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

We will review the proposed label separately.

9.3 Advisory Committee Meeting

Not Applicable

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/s/

JOHN M SHARRETTS
05/26/2017

MARINA ZEMSKOVA
05/26/2017