CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208418Orig1s000

CLINICAL REVIEW(S)

Division Director Memorandum

Date	*See Stamp Date*
From	Jean-Marc Guettier, MD
Subject	Division Director
NDA/BLA # Supplement#	NDA 208418
Applicant	Fresenius Kabi
Date of Submission	5/16/2016
PDUFA Goal Date	6/16/2017
Proprietary Name / Established (USAN) names	Calcium Gluconate Injection
Dosage forms / Strength	Calcium Gluconate Injection, 1g/10 ml and 5 g/50 ml vial Calcium Gluconate Injection, Pharmacy Bulk Package, 10 g/100 ml vial
Proposed Indication	(b) (4)
Approved Indication	*is indicated for pediatric and adult patients for the treatment of acute symptomatic hypocalcemia*
Recommended:	Approval

On May 16, 2016 Fresenius Kabi submitted a New Drug Application (NDA) for *Calcium Gluconate Injection* pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The NDA relies exclusively on data derived from the published literature to support the claim that intravenous administration of calcium gluconate is safe and effective for the treatment of acute symptomatic hypocalcemia. The clinical data in the application were reviewed by Drs. Singh and Sharretts. Dr. Zemskova, summarized the salient findings across all review disciplines in her memorandum. No CMC, pharmacology/toxicology, clinical pharmacology, microbiology, or efficacy and safety issues that would preclude approval were identified. This memorandum provides concurrence with Drs. Sharrets and Zemskova's benefit-risk assessment and decision to recommend approval.

Calcium Gluconate Injection, USP 10%, is a marketed unapproved drug[1] which is widely used, in the acute care setting, to treat severe, acute, symptomatic hypocalcemia and prevent the life-threatening complications that result from this disorder (i.e., focal or generalized seizures, QT

[1] i.e., a drug available in the United States that lacks required FDA approval for marketing.

prolongation, arrhythmias, and laryngeal spasm). Severe acute symptomatic hypocalcemia generally arises when calcium drops rapidly to low levels.
The fact that calcium is an essential body mineral and that severe acute hypocalcemia follows a well understood and predictable clinical course was considered in the overall interpretability of the published literature submitted to support efficacy. Calcium levels and clinical manifestations of severe acute hypocalcemia do not correct spontaneously without; rapid resolution of the underlying cause[2] or rapid calcium replacement. In addition, the outcomes (i.e., measures of circulating calcium concentration) used in most studies to establish the benefit of *Calcium Gluconate Injection* (i.e., measures of serum calcium concentration) were deemed self-evident and face-valid. That is, clinical manifestations of severe acute hypocalcemia are intimately linked to serum calcium concentration and raising serum calcium concentration from low to normal levels has the effect of reducing symptoms of severe hypocalcemia and risks of end-organ complications attributed to hypocalcemia.

Dr. Sharretts reviewed 48 publications submitted to support the efficacy determination and concludes that the published literature provides the necessary evidence to establish that *Calcium Gluconate Injection* is an effective treatment for acute symptomatic hypocalcemia regardless of etiology in both pediatric and adult patients (refer to his review for details). Dr. Sharretts also reviewed the justification for the dosage proposed for adult and pediatric patients. The adult and pediatric dosage for bolus and continuous infusion was determined to; fall within the range of doses studied in the published literature and to be consistent with doses of calcium gluconate recommended by professional societies, and with doses currently used in acute care settings to correct severe hypocalcemia.

Dr. Sharretts has summarized the risks associated with use of calcium gluconate. The most serious risk is the development of cardiac arrhythmias associated with rapid infusion of a concentrated solution in the circulation. This risk can be adequately mitigated by diluting the solution prior to infusion, by administering the solution at a slow infusion rate, and by cardiac monitoring during the infusion. Other more common and less serious complications are due to extravasation of calcium gluconate at the site of infusion which can result in injection site reactions, soft tissue inflammation, local pain, skin necrosis and calcinosis cutis. Dilution of calcium gluconate prior to administration and administration of the drug through large veins decrease the risks associated with extravasation.

Overall, the benefits of using calcium gluconate for the proposed intended use do not outweigh the risks. Raising serum calcium levels from low to normal levels in symptomatic individual will

[2] Most causes of severe acute hypocalcemia cannot be rapidly resolved.

alleviate the symptoms of severe hypocalcemia and reduce the risks of tetany, seizures and arrhythmias. The risks associated with the use of the product are well-understood and can be mitigated and monitored. No CMC, pharmacology/toxicology, clinical pharmacology or other review issues were identified that would preclude approval. The applicant has provided the required evidence necessary to comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and I concur with the Team's recommendation to recommend approval of this product.

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/s/

JEAN-MARC P GUETTIER
06/15/2017

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208418
Priority or Standard	Standard
Submit Date(s)	May 16, 2016
Received Date(s)	May 16, 2016
PDUFA Goal Date	June 16, 2017
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 430.373 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 (b) (4) injection into perivascular tissues, (b) (4), (b) (4) peripheral vasodilation, decreased blood pressure, and burning sensation (b) (4).

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 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.

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
Martin 1990	Randomized, controlled trial Adult patients with hypocalcemia during the anhepatic stage of liver transplant: 7 calcium gluconate vs 8 calcium chloride	Bolus: 1800-3000 mg **(30 mg/kg)**	167-280 mg 2.8 mg/kg	Ionized calcium increased by 0.60 mg/dL (0.15 mmol/L) above nadir at 10 minutes Ionized calcium increased by 0.32 mg/dL above nadir in the calcium chloride arm
Dickerson 2007a	Single arm study 25 adult patients with hypocalcemia and critical illness due to trauma 4000 mg: 15 2000 mg: 10	Infusion: **4000 mg/day** In 50-150 mL over 4 hours **2000 mg/day** In 50-150 mL over 2 hours	372 mg/day 186 mg/day	Ionized calcium increased by 0.96 mg/dL (0.24 mmol/L) at one day Ionized calcium increased by 0.44 mg/dL (0.11 mmol/L at one day
Bold text in dose columns indicates doses described in the article text.				

Dickerson 2007b	Single arm study 20 adult patient with hypocalcemia and critical illness due to trauma	Infusion: **4000 mg/day** In 50-150 mL over 4 hours	372 mg/day	Ionized calcium increased by 1.04 mg/dL (0.26 mmol/L) at one day
Dickerson 2005	Single arm study 37 adult patients with hypocalcemia and critical illness due to trauma 1000 mg: 8 2000 mg: 21 3000 mg: 2 4000 mg: 1	Infusion: **1000 mg/day** **2000 mg/day** **3000 mg/day** **4000 mg/day**	93 mg/day 186 mg/day 279 mg/day 372 mg/day	Ionized calcium at one day increased by about: 0.32 mg/dL (0.08 mmol/L) for the 1000 mg dose and 0.64 mg/dL (0.16 mmol/L) for the 2000 mg dose; insufficient data for 3000-4000 mg
Steele 2013	Retrospective study 539 adult patients with hypocalcemia and critical illness	Bolus: **1000 mg/day** 10 mL in 20 mL over 30 minutes daily for 4 days	93 mg	Ionized calcium increased by 0.20-0.72 mg/dL (0.05-0.18 mmol/L) after one day; not all subjects received calcium on days 2-4
Loke 2009	Observational study 36 patients with chronic kidney disease and secondary hyperparathyroidism post parathyroidectomy	Infusion: 10800-21600 mg/day **(450-900 mg/hour)**	1008-2016 mg/day 42-84 mg/hour	Treatment guidance based on model derived from observational study
Cooper 2008	Review article Acute symptomatic hypocalcemia	Bolus: **1000 mg** in 50-100 mL D5W over 10 minutes x 1-2 doses	93 mg	

		Infusion: 12000 mg/day 500 mg/hour **(10 grams in 1 Liter D5W or NS [10 mg/mL] at 50 mL/hour)**	1128 mg/day 47 mg/hour 0.93 mg/mL at 50 mL/hour	100 mg/kg calcium gluconate = (6000-10000 mg) over 4-6 hours increases serum calcium by 1.2 to 2.0 mg/dL (0.3 to 0.5 mmol/L)
French 2012	Review article Severe symptomatic hypocalcemia Mild symptomatic hypocalcemia: ionized calcium 4.0-4.8 mg/dL (1.0-1.2 mmol/L) Moderate to severe hypocalcemia: ionized calcium < 4.0 mg/dL (1.0 mmol/L)	Bolus: **1000-2000 mg** over 10 minutes, repeat hourly **1000-2000 mg** over 2 hours **4000 mg** over 4 hours	93-186 mg 93-86 mg 372 mg	Recommended doses normalize ionized calcium levels in the majority of patients. The author recommends checking ionized calcium level 6-10 hours after infusion
Kelly 2013	Review article	Bolus: 1075-2150 mg Infusion: 7800-23200 mg/day (5.4-16.1 mg/kg/hour 130-386 mg/kg/day)	**100-200 mg Over 10-20 minutes** **0.5-1.5 mg/kg/hour** 12-36 mg/kg/day	1-2 mg/kg elemental calcium raises serum calcium by 0.5 to 1.0 mg/dL

American Heart Association 2005	Guideline Acute symptomatic hypocalcemia	Bolus: 1000-2000 mg over 10 min Infusion: 6450-16130 mg/day (108-161 mg/kg at 5.4-21.5 mg/kg/hour) 5800-7700 mg in 500-1000 mL D5W (5.8-15.4 mg/mL)	**93-186 mg** 600 to 1500 mg **10-15 mg/kg** at 0.5-2 mg/kg/hour 540-720 mg in 500-1000 mL D5W (0.54-1.44 mg/mL)	No efficacy data
Society for Endocrinology (Turner) 2016	Guideline	Bolus: **1000-2000 mg** in 50-100 mL D5W (10-40 mg/mL) over 10 minutes Infusion: 12000-24000 mg/day **(500-1000 mg/hour 10000 mg in 1000 mL NS or D5W [10 mg/mL] at 50-100 mL/hour)**	93-186 mg 1116-2232 mg/day 46.5-93 mg/hour 930 mg in 1000 mL (0.93 mg/mL) at 50-100 mL/hr	No efficacy data
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
Morrell 1984	Non-randomized study Pediatric patients undergoing cardiopulmonary bypass with either heparin or citrate-phosphate-dextrose anticoagulation (CPD)	Heparin group: No calcium CPD arms: **500 mg** per unit of blood transfused	 46.5 mg/unit	Calcium infusion mitigated the relative decrease in ionized calcium associated with CPD compared to baseline (article reported percent of baseline value, but not raw ionized calcium values)

		1000 mg/unit **1000 mg**/unit plus **250 mg/L** circulating blood volume	93 mg/unit 93 mg/unit plus 23.2 mg/L	
Jaffe 1972	Case series 14 pediatric patients with acute leukemia, 16 episodes of hypocalcemia, ages and weights not reported	Bolus: **1000 mg** 20-100 mg/kg (estimated weights 10-50 kg)	93 mg	12/16 subjects "responded" to treatment (biochemically) within 30 minutes to 7 days of therapy. 11 subjects experienced rapid symptom improvement.
Thakur 2008	Case series 3 pediatric patients with hypocalcemic tetany due to paromomycin, weights not reported, ages 4, 10, and 15	Bolus: 30-125 mg/kg **(1000-2000 mg)** (weights estimated based on ages)	3-12 mg/kg 93-186 mg	No biochemical efficacy data All three patients experienced improvement in symptoms of tetany (carpopedal spasm)
Helikson 1997	Case report 3-year-old (18 kg) with hypocalcemia due to hyperphosphatemia	Bolus: 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
Hebbar 2006	Case report 7-week-old with hypocalcemia due to hyperphosphatemia	Bolus: **85 mg/kg** x 3 doses **(500 mg x 3)** Dose administered over 30 minutes	8 mg/kg x 3 46.5 mg x 3	Increased ionized calcium more than 1.5 mg/dL at about 8 hours Tetany and respiratory failure resolved following calcium infusions

Kossoff 2002	Case report 34-day old with hypocalcemia due to Vitamin D deficiency	Infusion: **75 mg/kg/day** x 3 days	7 mg/kg/day x 3 days	Ionized calcium increased 1.72 mg/dL (0.43 mmol/L) after three days Seizures resolved on day 4
Geffner 1980	Case report 15-month old with hypocalcemia due to hyperphosphatemia	Bolus: **1700 mg** 150 mg/kg over 5 minutes and then Infusion: **3300 mg** 300 mg/kg/day (weight estimated based on age)	14 mg/kg 27.9 mg/kg/day	Total calcium increased about 4.0 mg/dL at 18 hours (from 4.5 mg/dL baseline to "normal") Mental status changes improved
Edmondson 1990	Case report 4-year old (11 kg) with hypocalcemia due to hyperphosphatemia	Bolus: 90 mg/kg **(1000 mg)**	8.5 mg/kg	Change in calcium level not reported Tetany manifested by tongue fasciculation and carpopedal spasm resolved with treatment
Raffaella 2009	Case report 5-year old with hypocalcemia due to tumor lysis	Infusion: **200-300 mg/kg/day**	18.6-27.9 mg/kg/day	Total calcium increased greater than 3.6 mg/dL (0.9 mmol/L) over 9 days
Latorre 1974	Case report 9-year old with hypocalcemia due to osteomalacia	Infusion: 1600 mg/kg/day	**15 mg/kg/day**	Calcium normalized over 6 weeks Bone density on x-ray improved

Devlin 1990	Case reports Two patients with hypocalcemia and atopic eczema, ages: 4 years, 10 months 7 years, 10 months	Infusion: 400 mg/kg/day (2900 mg/day) Infusion: 40 mg/kg/day **(1000 mg/day)** (weights estimated based on ages)	16 mg/kg/day 270 mg/day **6.75 mmol/day** 3.7 mg/kg/day 93 mg/day	Calcium levels not reported for either case, safety reports only
Zhou 2009	Review article	Bolus: 50-200 mg/kg Infusion: **200 mg/kg/day**	**5-20 mg/kg** over 10-20 minutes 18.6 mg/kg/day	
Kelly 2013	Review article	Bolus: 11-22 mg/kg Infusion: 264-792 mg/kg/day 11-33 mg/kg/hour	**1-2 mg/kg** over 5-10 minutes 24-72 mg/kg/day **1-3 mg/kg/hour**	Recommended bolus plus infusion increases serum calcium 0.5 to 1.0 mg/dL
Hospira 2009	Calcium chloride (NDA 021117) prescribing information Pediatric dosing	Bolus: 29-54 mg/kg	2.7-5.0 mg/kg **0.136-0.252 mEq/kg**	
American Academy of Pediatrics 1998	Guideline	Bolus: **60 mg/kg**	5.6 mg/kg	

Taketomo 2014	Dosage Handbook Textbook	Bolus: **100-200 mg/kg** Infusion: **200-800 mg/kg/day**	9.3-18.6 mg/kg 18.6-74.4 mg/kg/day	

Clinical Efficacy Studies in Neonatal Patients (≤ 1 month)				
Source	**Study Design and Population**	**Dose: Calcium Gluconate**	**Dose: Elemental Calcium**	**Efficacy Results**
Brown 1981	Randomized, controlled trial Preterm neonates with hypocalcemia 18 High dose vs 18 Low dose vs 11 No treatment	Continuous infusion or divided doses every 6 hours: **600 mg/kg/day** **400 mg/kg/day** Bolus over 1-2 minutes	 55.8 mg/kg/day 37.2 mg/kg/day	At 24 hours, ionized calcium increased by: 0.72 mg/dL (0.18 mmol/L) 0.39 mg/dL (0.10 mmol/L)
Porcelli 1995	Randomized, placebo controlled trial Preterm neonates with symptomatic hypocalcemia 22 calcium gluconate vs 21 Placebo	Bolus: **100 mg/kg**	9.3 mg/kg	Ionized calcium increased 0.5 mg/dL (0.12 mmol/L) at 3-6 hours Symptom scores decreased in subjects treated with calcium gluconate compared to placebo

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)
Roberts 1977	Case series 4 neonates with hypocalcemia	Bolus: 62-195 mg/kg	5.8-18 mg/kg	No calcium efficacy data (safety reports only)
Al-Wahab 2001	Case report 3-day old infant with 2:1 AV block, serum calcium 1.01 mmol/L (4.04 mg/dL) 0.1 mmol calcium gluconate = 43 mg or 0.43 mL (100 mg/mL) *Article reports: 0.1 mmol = 0.5 mL	Bolus: 43 mg/kg and then (*50 mg/kg and then) Infusion: 430 mg/kg/day (*500 mg/kg/day)	4 mg/kg **(0.1 mmol/kg)** and then 40 mg/kg/day **(1 mmol/kg/day)**	Ionized calcium increased by 0.12 mmol/L at 2 hours (0.48 mg/dL) and 0.25 mmol/L (1 mg/dL) at 4 hours Bradycardia and 2:1 AV block resolved after infusion
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
Jain 2010	Review and guideline	Bolus: **200 mg/kg** over 10 minutes Infusion: 860 mg/kg/day	18.6 mg/kg **80 mg/kg/day x 48 hr and then** **40 mg/kg/day x 24 hr**	No calcium efficacy data
Mimouni 1994	Review article	Bolus: 194 mg/kg Infusion: 807 mg/kg/day	**18 mg/kg** **75 mg/kg/day**	No efficacy data
Zhou 2009	Review article	Bolus: 200 mg/kg Infusion: **500 mg/kg/day**	**20 mg/kg** over 10-20 minutes 46.5 mg/kg/day	

Corporate 2014	Drug Facts and Comparisons Textbook	Bolus: **200 mg** (maximum dose)	18.6 mg	No efficacy data
Cloherty 2012	Manual of Neonatal Care Textbook	Bolus: **100-200 mg/kg** over 10-15 minutes Infusion: 430-538 mg/kg/day	9.3-18.6 mg/kg **40-50 mg/kg/day**	No efficacy data
Taketomo 2014	Pediatric & Neonatal Dosing Handbook (Textbook)	Bolus: **100-200 mg/kg** over 5-10 min Infusion: **500-800 mg/kg/day**	9.3-18.6 mg/kg 46.5-74.5 mg/kg/day	No efficacy data

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.*

Martin, 1990 (*Anesthesiology*. 1990; 73: 62-65)

Title: *Ionization and Hemodynamic Effects of Calcium Chloride and Calcium Gluconate in the Absence of Hepatic Function*

Design: Randomized, active control trial

Objectives: To compare the effect of calcium gluconate to calcium chloride in the treatment of hypocalcemia during the anhepatic phase of liver transplantation.

Study Population:
15 male and female adult patients undergoing liver transplant

- Calcium chloride: 8
- Calcium gluconate: 7

Inclusion and Exclusion Criteria

- Not specified

Withdrawal Criteria

- Investigators enrolled but excluded two subjects who required vasopressors, and seven subjects with hypocalcemia before or after the anhepatic stage

Schedule and Duration:
The study consisted of an undefined screening period, monitoring prior to the anhepatic period, and a treatment period lasting approximately 10 minutes after the onset of hypocalcemia (nadir). Investigators collected blood samples every 30 to 60 minutes prior to the anhepatic stage, and at 30 seconds, and 1, 3, 5 and 10 minutes after calcium infusion.

Study Treatments:
A single dose of approximately 0.136 mEq/kg elemental calcium (2.73 mg/kg)

- Calcium gluconate 30 mg/kg
- Calcium chloride 10 mg/kg

Statistical Considerations:
The article did not specify a primary endpoint. Investigators used analysis of variance for repeated measures and compared differences between groups with the Student-Newman-Keuls test.

Summary of Efficacy and Safety Findings:
Baseline characteristics were similar between arms. Mean nadir ionized calcium was 0.64 ± 0.08 mmol/L (2.56 mg/dL) in the calcium chloride arm and 0.74 ± 0.11 (2.96 mg/dL). At one minute, mean ionized calcium increased to 0.98 ± 0.14 mmol/L (3.92 mg/dL) in the calcium chloride arm and 1.05 ± 0.10 mmol/L (4.20 mg/dL) in the calcium gluconate arm. Ionized calcium remained above nadir at both 5 and 10 minutes in both arms.

Table 3: *Serum Calcium Values Before and After Calcium Infusion (Martin 1990)*

Ionized calcium (mmol/L)	**Calcium chloride**		**Calcium gluconate**	
Baseline	1.00 ± 0.10		1.00 ± 0.10	
Nadir (Time 0)	0.68 ± 0.14		0.74 ± 0.10	
1 minute	0.98 ± 0.14	+ 0.30	1.04 ± 0.10	+ 0.30
5 minutes	0.83 ± 0.08	+ 0.15	0.93 ± 0.10	+ 0.19
10 minutes	0.76 ± 0.07	+ 0.08	0.89 ± 0.09	+ 0.15
Values represent mean and standard deviation				

The article did not report areas under the plasma concentration time curve (AUC). The article reported no significant difference in heart rate, mean arterial pressure, or other hemodynamic variables.

> *Reviewer comment:*
> *Calcium gluconate 30 mg/kg increased serum ionized calcium 0.15 mmol/L (0.60 mg/dL) above baseline after 10 minutes in patient with hypocalcemia during the anhepatic stage of liver transplant.*

Dickerson 2007a (*Nutrition*. 2007. 23: 9-15)

Title: *Dose-dependent Characteristics of Intravenous Calcium Therapy for Hypocalcemic Critically Ill Trauma Patients Receiving Specialized Nutritional Support*

Summary: This was a single arm study involving 25 critically ill, adult, multiple trauma patients within 90-120% of ideal body weight (IBW) with hypocalcemia and normal kidney function. The study population included 16 males, the mean age was 44 ± 19, and the mean weight was 70.6 ± 10.9 kg.

Fifteen subjects with ionized calcium 1.0-1.12 mmol/L (4.0-4.48 mg/dL) received calcium gluconate 2000 mg at a rate of 1000 mg per hour. Among these subjects, the ionized calcium increased from 1.07 ± 0.05 at baseline to 1.18 ± 0.05 mmol/L (mean ± SD) at one day. Ten subjects with ionized calcium less than 1 mmol/L at baseline received calcium gluconate 4000 mg over four hours. Among these subjects, the ionized calcium increased from 0.92 ± 0.08 at baseline to 1.16 ± 0.11 mmol/L. Calcium levels achieved plateau without further decline by 10 hours.

> *Reviewer comment:*
> *Infusion of calcium gluconate 2000 mg/day increased ionized calcium 0.11 mmol/L (0.44 mg/dL) above baseline after one day in critically ill patients with hypocalcemia. Infusion of calcium gluconate 4000 mg/day increased ionized calcium 0.24 mmol/L (0.96 mg/dL) above baseline after one day in patients with hypocalcemia.*

Dickerson 2007b (*JPEN J Parenter Enteral Nutr*. 2007; 31: 228-33)

Title: *Treatment of Moderate to Severe Acute Hypocalcemia in Critically Ill Trauma Patients*

Summary: This was a single arm study involving 20 critically ill, adult, multiple trauma patients with hypocalcemia and normal kidney function. The population included 15 male subjects, the mean age was 35 ± 14, and the mean weight was 84 ± 20 kg. All

subjects had baseline ionized calcium less than 1 mmol/L (4 mg/dL) and received calcium gluconate 4000 mg over four hours. The mean ionized calcium increased from 0.90 ± 0.08 at baseline to 1.16 ± 0.11 mmol/L at one day. Nineteen of twenty subjects achieved ionized calcium level greater than 1 mmol/L (4 mg/dL) and 14 of these achieved a level above 1.12 mmol/L (4.48 mg/dL). Two subjects experienced mild hyperkalemia (1.34 mmol/L and 1.38 mmol/L).

> *Reviewer comment:*
> *Infusion of calcium gluconate 4000 mg/day increased serum ionized calcium 0.26 mmol/L (1.04 mg/dL) above baseline after one day in critically ill patients with hypocalcemia.*

Dickerson 2005 (*JPEN J Parenter Enteral Nutr*. 2005; 29: 436-41)

Title: *Treatment of Acute Hypocalcemia in Critically Ill Multiple-trauma Patients*

Summary: This was a single arm study of 37 critically ill, adult, multiple trauma patients with hypocalcemia. Subjects received calcium gluconate 1000-2000 mg if the baseline ionized calcium was 1.0-1.12 mmol/L. Among these subjects, 23/29 experienced normal ionized calcium one day after infusion, and the mean ionized calcium increased from 1.08 ± 0.03 at baseline to 1.18 ± 0.07 mmol/L at one day. Subjects received 2000-4000 mg of calcium gluconate if the baseline ionized calcium was less than 1 mmol/L at baseline. Among these subjects, 3/8 experienced normal ionized calcium one day after the infusion, and the mean ionized calcium increased from 0.93 ± 0.09 at baseline to 1.13 ± 0.12 mmol/L at one day. Eight subjects received 1000 mg of calcium gluconate, 21 subjects received 2000 mg, two subjects received 3000 mg, and one subject received 4000 mg. Overall, the mean ionized calcium increased from 1.05 ± 0.08 to 1.17 ± 0.08 mmol/L. The article did not report precise values, but median increase was about 0.08 mmol/L for the 1000 mg dose and 0.16 mmol/L for the 2000 mg dose from a scatter plot by dose.

> *Reviewer comment:*
> *Infusion of calcium gluconate 1000-2000 mg/day in critically ill patients with hypocalcemia increased serum ionized calcium 0.08-0.16 mmol/L (0.32-0.64 mg/dL) above baseline after one day.*

Steele 2013 (*Critical Care*. 2013: 17: R106)

Title: *Assessment and Clinical Course of Hypocalcemia in Critical Illness*

Summary: This was a retrospective study of patients derived from a prospective, non-interventional study database. Subjects in the intensive care units of a single institution

received calcium gluconate 1000 mg/day per protocol if the adjusted serum calcium was less than 2.2 mmol/L (8.8 mg/dL). Among 1038 admissions, 539 patients experienced ionized calcium less than 1.1 mmol/L, and 60 patients experienced ionized calcium less than 0.9 mmol/L. The median age of hypocalcemic patients was 61, and 298 patients (55%) were male. All subjects received calcium on Day 1. Subjects did not receive calcium on subsequent days if the corrected calcium was normal. Ionized calcium increased 0.18 mmol/L (0.72 mg/dL) on the first day in the subset of patients with ionized calcium less than 0.9 mmol/L at baseline, and 0.05 mmol/L (0.20 mg/dL) among patients with ionized calcium 0.9-1.1 mmol/L at baseline.

Table 4: *Mean Ionized Calcium (mmol/L) by Day and Group (Steele 2013)*

	Baseline ionized calcium (mmol/L)		
Day	**Calcium < 0.9**	**0.9-1.1**	**1.1-1.3 (no treatment)**
1	0.82	1.03	1.15
2	1.00	1.08	1.14
3	1.07	1.11	1.15
4	1.11	1.13	1.15

Reviewer comment:
Investigators did not design the observational protocol to assess the effect of calcium gluconate infusion on patients with hypocalcemia over four days. Hypocalcemic patients treated with calcium gluconate on Day 1 experienced an increase in ionized calcium of 0.05 to 0.18 mmol/L (0.20 to 0.72 mg/dL) above baseline after one day.

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.

Kossoff 2002 (*J Child Neurol*. 2002: 17: 236-239)

Title: *Neonatal Hypocalcemic Seizures: Case Report and Literature Review*

Summary: This was a case report of a 34-day old infant with seizures and hypocalcemia due to severe vitamin D deficiency. At baseline, the serum calcium was 6.1 mg/dL (normal range: 8.4-10.5), ionized calcium was 0.75 mmol/L (1.13-1.32), and phosphorus was 8.8 mg/dL (3.2-6.3). The patient received calcium gluconate 75 mg/kg/day for three days. The ionized calcium increased to 1.18 mmol/L the third day of treatment, and the patient converted to oral calcium and vitamin D supplements. Seizures resolved on Day 4 of treatment.

Reviewer comment:
Calcium gluconate 75 mg/kg/day increased ionized calcium by 0.43 mmol/L (1.72 mg/dL) above baseline after three days in a pediatric patient with hypocalcemia.

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.

Hebbar 2006 (*Pediatr Emerg Care*. 2006; 22:118-120)

Title: *Severe Hypocalcemic Tetany and Respiratory Failure in an Infant Given Oral Phosphate Soda*

Summary: This was a case report of a seven-week-old patient treated with oral phosphate laxative who presented with serum phosphorus 22.6 mg/dL (normal: 3.4-5.9), ionized calcium 1.5 mg/dL (4.5-5.5), and total calcium 4.4 mg/dL (8.9-10.3). The patient received three doses of calcium gluconate 500 mg (85 mg/kg), each over 30 minutes until the "ionized calcium concentration was greater than 3.0 mg/dL," approximately eight hours later. The patient received oral calcium carbonate 250 mg every 6 hours concurrently.

> *Reviewer comment:*
> *Calcium gluconate 255 mg/kg increased serum ionized calcium greater than 1.5 mg/dL above baseline in a pediatric patient with hypocalcemia and hyperphosphatemia.*

Geffner 1980 (*Am J Dis Child*. 1980: 134: 509-510)

Title: *Phosphate Poisoning Complicating Treatment for Iron Ingestion*

Summary: This was a case report involving a 15-month old child with phosphate-induced hypocalcemia, caused by hypertonic phosphate therapy for iron intoxication. The patient presented with serum total calcium 4.5 mg/dL and phosphorus 24.6 mg/dL (normal ranges not reported). QT_c was 0.50 seconds. The patient received intravenous calcium gluconate, 1700 mg bolus, and a total of 5000 mg over 18 hours (approximately 300 mg/kg/day based on the median weight for a 15-month old). The calcium and phosphorus levels were reportedly normal at 18 hours.

> *Reviewer comment:*
> *Calcium gluconate 300 mg/kg/day increased serum total calcium by at least 4.0 mg/dL above baseline after 18 hours in a pediatric patient with hypocalcemia.*

Raffaella 2009 (*Ped Derm*. 2009; 26: 311-315)

Title: *Successful Treatment of Severe Iatrogenic Calcinosis Cutis with Intravenous Sodium Thiosulfate in a Child Affected by T-Acute Lymphoblastic Leukemia*

Summary: This was a case report of a five-year-old boy with tumor lysis syndrome related to treatment for acute lymphoblastic anemia. The article did not report the baseline calcium level, but the total serum calcium was 1.30 mmol/L (2.20-2.70) shortly

after initiation of treatment. The patient received calcium gluconate infusion 200-300 mg/kg/day for nine days, and then 50-100 mg/kg/day for six days. The calcium level reportedly normalized, but the article did not report the value. As the title notes, the patient developed subcutaneous calcification which resolved over the course of about six months.

> *Reviewer comment:*
> *Calcium gluconate 200-300 mg/kg/day increased total serum calcium at least 0.90 mmol/L (3.6 mg/dL) above baseline after about nine days in a patient with hypocalcemia due to tumor lysis syndrome.*

Studies of Neonatal Patients:

Brown 1981 (*Am J Dis Child*. 1981; 135: 24-28)

Title: *Treatment of Early-Onset Neonatal Hypocalcemia*

Design: 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:
50 male and female pre-term infants with hypocalcemia
Completed 24-hours: 47 (at least one assessment)

- High dose calcium gluconate: 18
  - Continuous infusion: 9
  - Bolus (intermittent): 9
- Low dose calcium gluconate: 18
  - Continuous infusion: 10
  - Bolus (intermittent): 8
- Control: 11

Inclusion Criteria

- Total serum calcium less than 7.0 mg/dL (1.75 mmol/L) OR
- Ionized serum calcium less than 3.5 mg/dL (0.88 mmol/L)

Exclusion Criteria

- Not specified

Withdrawal Criteria

- Death
- Treatment failure (symptomatic, requiring additional parenteral calcium)

Schedule and Duration:
The study consisted of an undefined screening period, a 48-hour treatment period, and final assessment at 72 hours.

Study Treatments:
- High dose calcium gluconate 54 mg/kg elemental calcium (600 mg/kg calcium gluconate) per day for 24 hours, and then 27 mg/kg elemental calcium (300 mg/kg calcium gluconate) per day for 24 hours (total 48 hours therapy)
    - Continuous infusion
    - Bolus (intermittent infusion) divided doses every 6 hours over 1-2 minutes
- Low dose calcium gluconate 18 mg/kg elemental calcium (200 mg/kg calcium gluconate) per day for 24 hours, and then 9 mg/kg elemental calcium (100 mg/kg calcium gluconate) per day for 24 hours
    - Continuous infusion
    - Bolus (intermittent infusion)
- Control (no parenteral calcium)

Statistical Considerations:
The article did not specify a primary endpoint. Investigators used two separate one-way analysis of variance analyses to compare serum calcium to baseline: one using dose as the independent variable, and the other using mode of therapy (continuous versus intermittent) as the independent variable. Investigators compared calcium values between arms at each time point with Students *t*-test.

Summary of Efficacy and Safety Findings:
Investigators enrolled 50 subjects, and withdrew three prior to the first assessment. The article did not report baseline demographics. In the control arm, serum ionized calcium was 2.53 ± 0.10 mg/dL (0.63 mmol/L) at baseline, and 2.69 ± 0.18 mg/dL (0.67 mmol/L) at 24 hours. In the high-dose arm, ionized calcium increased from 2.59 ± 0.10 mg/dL (0.65 mmol/L) at baseline to 3.31 ± 0.14 mg/dL (0.83 mmol/L) at 24 hours ($p < 0.05$ versus baseline and versus control). In the low-dose arm, calcium increased from baseline, but the result was not significantly different from control. In the continuous infusion arm, ionized calcium increased from 2.63 ± 0.08 mg/dL to 3.27 ± 0.14 mg/dL ($p < 0.05$ versus baseline and versus control). In the intermittent-dose arm, calcium increased from baseline, but the result was not significantly different from control.

The article did not report precise values for total serum calcium, but graphically presented results were concordant with those for ionized calcium. Serum calcium increased from approximately 6.3 mg/dL (1.6 mmol/L) to about 8.1 mg/dL (2.0 mmol/L) in the high-dose arm compared to no significant change in the control arm at 24 hours. Results at 48 and 72 hours are not interpretable due to the high dropout rate. Investigators reported data only for completers.

Table 6: *Serum Ionized Calcium Before and After Calcium Infusion (Brown 1981)*

	Ionized Calcium (mg/dL)				
Time	**Control**	**High dose**	**Low Dose**	**Continuous**	**Bolus**
Baseline	2.53 ± 0.10	2.59 ± 0.10	2.59 ± 0.08	2.63 ± 0.08	2.55 ± 0.10
24 hours	2.69 ± 0.18	3.31 ± 0.14	2.98 ± 0.13	3.27 ± 0.14	3.00 ± 0.13
N	11	18	18	19	17

Reviewer comment:
Calcium gluconate 600 mg/kg per day resulted in increase in ionized serum calcium compared to control at 24 hours. Calcium gluconate 300 mg/kg per day was not superior to placebo in this study.

Porcelli, 1995 (*Am J Perinatol*. 1995; 12: 18-21)

Title: *Effect of Single Dose Calcium Gluconate Infusion in Hypocalcemic Preterm Infants*

Design: Randomized, double blind, placebo control trial

Objectives: To evaluate the effect of a calcium gluconate infusion on serum calcium concentration and clinical signs of hypocalcemia in preterm neonates with hypocalcemia

Population:
43 male and female preterm infants with hypocalcemia
- Calcium gluconate: 22
- Control: 21

Inclusion Criteria
- Gestational age 36 weeks or less
- Age less than 4 hours
- Total serum calcium 7.0 mg/dL (1.75 mmol/L) or less

Exclusion Criteria
- Prenatal maternal magnesium therapy
- Suspected disorders of maternal or fetal calcium metabolism
- Infant blood transfusion
- Infant calcium administration for other medical indication (hypokalemia)

Schedule and Duration:
The study consisted of a screening period within four hours of birth, a 30- to 60-minute treatment period, and final assessments three to six hours following treatment.

Study Treatments:
Intravenous infusions of over 30 to 60 minutes:

- Calcium gluconate 100 mg/kg
- Placebo (normal saline)

Investigators evaluated within group change (change from baseline) in total serum calcium, ionized serum calcium, and hypocalcemic sign score for each treatment arm.

Statistical Considerations:
The article did not specify a primary endpoint. The article reported comparison of pre- and post-treatment serum calcium values using Student's paired t-test, and comparison of pre- and post-treatment hypocalcemic sign scores using the Friedman test for nonparametric paired data.

Summary of Efficacy and Safety Findings:
Investigators enrolled 43 subjects, 22 assigned to calcium gluconate and 21 to placebo, all of whom completed the study. Baseline demographic characteristics were similar between arms. Total and ionized serum calcium values in the placebo arm were unchanged from baseline to the final value. Total calcium in the calcium gluconate group increased from 1.58 ± 0.03 mmol/L to 1.70 ± 0.05 mmol/L (p = 0.001) after infusion, and ionized calcium increased from 0.67 ± 0.03 mmol/L to 0.80 ± 0.02 mmol/L (p = 0.002). Among 23 subjects with hypocalcemia sign score greater than zero at baseline (Three component score, range 0-9), the score was unchanged in the placebo arm, and decreased from 2.1 ± 0.5 at baseline to 0.9 ± 0.2 after infusion in the calcium gluconate arm. Investigators reported no adverse events.

> *Reviewer comment:*
> *Calcium gluconate infusion 100 mg/kg increased ionized serum calcium 0.13 mmol/L (0.52 mg/dL) above baseline after three to six hours in neonatal patients with hypocalcemia.*

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					
Dickerson 2005	8	1000 mg	1 hour	0.32	24 hours
Steele 2013	539	1000 mg	30 minutes	0.20-0.72	24 hours
Dickerson 2007a	10	2000 mg	2 hours	0.44	24 hours
Dickerson 2005	21	2000 mg	2 hours	0.64	24 hours
Martin 1990	7	1800-3000 mg	Bolus—NS	0.60	10 minutes
Dickerson 2007a	15	4000 mg	4 hours	0.96	24 hours
Dickerson 2007b	20	4000 mg	4 hours	1.04	24 hours

Pediatric Patients Ages (> 1 month to < 17 years)					
Broner 1984	20	29 mg/kg	Bolus–NS	0.37	30 minutes
Kossoff 2002	1	75 mg/kg	Bolus—NS	1.72	3 days
Helikson 1997	1	111 mg/kg	20-30 minutes	1.0	6 hours
Hebbar 2006	1	250 mg/kg	8 hours	1.5	8 hours
Geffner 1980	1	300 mg/kg	18 hours	4.0*	18 hours
Raffaella 2009	1	300 mg/kg	24 hours	3.6*	9 days
*Total serum calcium					

Neonatal Patients (≤ 1 month)					
Porcelli 1995	22	100 mg/kg	30-60 minutes	0.5	3-6 hours
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
Brown 1981	18	400 mg/kg	24 hours	0.39	24 hours
Brown 1981	18	600 mg/kg	24 hours	0.72	24 hours
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**
Martin 1990	7	30 mg/kg 1800-3000 mg	NS	NS	NS
Steele 2013	539	1000 mg	33 mg/mL	30 minutes	33 mg/min 2000 mg/hour
Dickerson 2005	8	1000 mg	NS	1 hour	17 mg/min 1000 mg/hour
Dickerson 2005	21	2000 mg		2 hours	17 mg/min 1000 mg/hour
Dickerson 2007a	10	2000 mg	13-40 mg/ mL	2 hours	17 mg/min 1000 mg/hour
Cooper 2008 *Review*	N/A	1000 mg	10-20 mg/mL	10 min	100 mg/min
French 2012 *Review*	N/A	1000-2000 mg	NS	10 min	100-200 mg/min
Kelly 2013 *Review*	N/A	1000-2000 mg	NS	10-20 min	100-200 mg/min
AHA 2005 *Guideline*	N/A	1000-2000 mg	NS	10 min	100-200 mg/min
Turner 2016 *Guideline*	N/A	1000-2000 mg	10-40 mg/mL	10 min	100-200 mg/min

Continuous infusions in adult patients					
Reference	**Subjects**	**Dose**	**Dilution**	**Time**	**Rate**
Dickerson 2005	2	3000 mg		3 hours	17 mg/min 1000 mg/hour
Dickerson 2005	1	4000 mg		4 hours	17 mg/mL 1000 mg/hour
Dickerson 2007a	15	4000 mg	26-80 mg/mL	4 hours	17 mg/min 1000 mg/hour
Dickerson 2007b	20	4000 mg	26-80 mg/mL	4 hours	17 mg/min 1000 mg/hour
Loke 2009	36	10000-20000 mg	NS	24 hours	7.5-15 mg/min 450-900 mg/hour
French 2012 *Review*	N/A	1000-4000 mg	NS	1-4 hours	17 mg/min 1000 mg/hour
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
Kelly 2013 *Review*	N/A	7800-23000 mg	NS	24 hours	5.4-16.1 mg/kg/hr 324-1610 mg/hr
Cooper 2008 *Review*	N/A	12000	10 mg/mL	24 hours	8.3 mg/min 500 mg/hour

Turner 2016 *Guideline*	N/A	12000-24000 mg	10 mg/mL	24 hours	8-17 mg/min 500-1000 mg/hour

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
Hebbar 2006	1	85 mg/kg (3 doses/8 hours)	NS	30 min	2.8 mg/kg/min 17 mg/min
Edmonson 1990	1	90 mg/kg	NS	NS	NS
Jaffe 1972	14	1000 mg (20-100 mg/kg)	NS	NS	NS
Thakur 2008	3	1000-2000 mg (30-125 mg/kg)	NS	NS	NS
Geffner 1980	1	1700 mg (150 mg/kg)	NS	5 min	340 mg/min
Kelly 2013 *Review*	N/A	11-22 mg/kg	NS	5-10 minutes	1.1-4.4 mg/kg/min
Hospira 2009 *Label*	N/A	29-54 mg/kg	NS	27 mg/minute elemental	290 mg/min
Zhou 2009 *Review*	N/A	50-200 mg/kg	NS	10-20 minutes	5-20 mg/kg/min
AAP 1998 *Guideline*	N/A	60 mg/kg	NS	NS	NS
Taketomo 2014 *Textbook*	N/A	100-200 mg/kg	NS	5-10 minutes	<200 mg/min

Continuous infusions in pediatric patients (> 1 month to < 17 years)					
Reference	**Subjects**	**Dose**	**Dilution**	**Time**	**Rate**
Kossoff 2002	1	75 mg/kg	NS	24 hours	3 mg/kg/hour
Devlin 1990	1	40-400 mg/kg	NS	24 hours	16 mg/kg/hour
Raffaella 2009	1	200-300 mg/kg	NS	24 hours	8-12 mg/kg/hour
Latorre 1974	1	1600 mg/kg	NS	24 hours	1 mg/kg/min 67 mg/kg/hour
Geffner 1980	1	3300 mg (300 mg/kg)	NS	24 hours	2.3 mg/min 137 mg/hour
Zhou 2009 *Review*	N/A	200 mg/kg		24 hours	

Kelly 2013 *Review*	N/A	264-792 mg/kg	NS	24 hours	11-33 mg/kg/hour
Taketomo 2014 *Textbook*	N/A	200-800 mg/kg	<50 mg/mL	24 hours	<200 mg/min

Bolus doses in neonatal patients (≤ 1 month)					
Reference	**Subjects**	**Dose**	**Dilution**	**Time**	**Rate**
Brown 1981	9	100 mg/kg Every 6 hours	NS	1-2 minutes	50-100 mg/kg/min
Porcelli 1995	22	100 mg/kg	NS	30-60 minutes	1.7-3.3 mg/kg/min 100-200 mg/kg/hr
Fishbein 1982	1	100 mg/kg	NS	NS	NS
Kurt 2006	1	100 mg/kg	NS	NS	NS
Brown 1981	9	150 mg/kg Every 6 hours	NS	1-2 minutes	50-100 mg/kg/min
Roberts 1977	4	62-195 mg/kg	NS	NS	NS
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
Mimouni 1994 *Review*	N/A	194 mg/kg	NS	10 minutes	19 mg/kg/min
Jain 2010 *Review*	N/A	200 mg/kg	50 mg/mL	10 minutes	20 mg/kg/min
Zhou 2009 *Review*	N/A	200 mg/kg	NS	10-20 minutes	10-20 mg/kg/min
Corporate 2014 *Textbook*	N/A	200 mg	NS	NS	NS
Cloherty 2012 *Textbook*	N/A	100-200 mg/kg	NS	10-15 minutes	7-20 mg/kg/min
Taketomo 2014 *Textbook*	N/A	100-200 mg/kg	NS	5-10 minutes	10-40 mg/kg/min

Continuous infusions in neonatal patients (≤ 1 month)					
Reference	**Subjects**	**Dose**	**Dilution**	**Time**	**Rate**
Brown 1981	9	400 mg/kg	NS	24 hours	17 mg/kg/hour
Scott 1984	9	400 mg/kg	NS	24 hours	17 mg/kg/hour
Al-Wahab 2001	1	430 mg/kg	NS	24 hours	18 mg/kg/hour
Fishbein 1982	1	500 mg/kg	NS	24 hours	21 mg/kg/hour
Brown 1981	9	600 mg/kg	NS	24 hours	25 mg/kg/hour
Jain 2010 *Review*	N/A	800 mg/kg	NS	24 hours	34 mg/kg/hour
Mimouni 1994 *Review*	N/A	75 mg/kg	NS	24 hours	3 mg/kg/hour
Zhou 2009 *Review*	N/A	500 mg/kg	NS	24 hours	21 mg/kg/hour
Cloherty 2012 *Textbook*	N/A	430-538 mg/kg	NS	24 hours	18-22 mg/kg/hour
Taketomo 2014 *Textbook*	N/A	500-800 mg/kg/day	<50 mg/mL	24 hours	21-34 mg/kg/hour

The Applicant proposes an initial bolus dose in adult patients of 1000 to 2000 mg, administered (b) (4) every (b) (4) six hours if needed. One clinical trial (*Martin, 1990*), three non-randomized studies (*Steele, 2013, Dickerson, 2005, Dickerson 2007*), review articles (*Cooper, 2008, French 2012, Kelly, 2013*), and guidelines (*American Heart Association, 2015, Turner, 2016*) support the proposed dose. One review article (*French, 2012*) recommends repeated boluses every six to eight hours following repeated determination of serum ionized calcium concentration.

Recommended infusion rates in reviews and guidelines vary considerably. The Applicant proposes a continuous infusion dose of (b) (4) mg/day, based on published guidelines (*American Heart Association, 2005*). This dose, however, represents only the recommended dilution (5.8-7.7 mg/mL). The guideline actually recommends a daily dose of 10-15 mg/kg *elemental calcium*, delivered at a rate of 0.5-2.0 mg/kg/hour of *elemental calcium* (5.4-21.5 mg/kg/hour) over 6-12 hours. *Kelly, 2005* recommends a similar regimen, starting with an infusion rate of 0.5 to 1.5 mg/kg/hour of elemental calcium. Four non-randomized studies (*Dickerson, 2005, Dickerson, 2007a, Dickerson, 2007b, and Loke 2009*) described intermittent or continuous infusions, administered at rates of 450-1000 mg/hour, or approximately 5-20 mg/kg/hour for most adults, consistent with the guidelines.

In pediatric patients, > 1 month to < 17 years, the Applicant proposes a single bolus dose of 29-(b) (4) mg/kg (b) (4) every (b) (4) six hours. The Applicant derived the bolus dose from the recommended dose of elemental calcium in the 10% Calcium Chloride Injection, USP Prescribing Information (*Hospira, 2009*). 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, Hebbar, 2006, Edmonson, 1990*). Guidelines support boluses up to 60 mg/kg (*American Academy of Pediatrics, 1998*). The literature does not clearly support (b) (4)

The Applicant proposes a continuous infusion rate of (b) (4) 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 (b) (4) and repeat doses every six hours. The literature, including randomized trials, supports the doses (*Brown, 1981, Porcelli, 1995, Scott, 1984, Bifano, 1989, Mirro, 1984, Venkataramen, 1985b, Brown, 1982, Salsburey, 1982*). Reviews generally recommend infusion over 10-20 minutes (*Mimouni, 1994, Jain, 2010, Zhou, 2009, Cloherty, 2012, Taketomo, 2014*).

The Applicant proposes a continuous infusion rate of (b) (4) in neonatal patients. Randomized trials support 400-600 mg/kg per day (*Brown, 1981, Scott, 1984*). Review articles and textbooks support 430-800 mg/kg per day (*Jain, 2010, Zhou, 2009, Cloherty, 2012, Taketomo, 2014*).

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 over 10-20 minutes	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 (b) (4)
Neonatal patients ages ≤ 1 month	100-200 mg/kg	100-200 mg/kg every 6 hours	17-33 mg/kg/hour (b) (4)

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

- For bolus doses, dilute 1000-2000 mg (1-2 mL) of Calcium Gluconate Injection (100 mg/mL) in 50-100 mL normal saline or 5% dextrose (10-40 mg/mL) prior to administration

- For continuous infusion, dilute 5800-10,000 mg (5.8-10 mL) of Calcium Gluconate Injection (100 mg/mL) in 1000 mL normal saline or 5% dextrose (5.8-10 mg/mL) prior to administration

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

- Monitor serum ionized calcium levels every 4-6 hours prior to repeat boluses or during continuous infusions of Calcium Gluconate Injection

  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 21,600 mg 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 150 mg/kg. Articles reported cumulative dosed up to 1600 mg/kg/day. 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 [(b) (4)] injection into perivascular tissues, [(b) (4)] peripheral vasodilation, decreased blood pressure, and burning sensation [(b) (4)] 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 20 mg/kg/minute in children and neonates (*Cooper, 2008, French, 2012, American Heart Association, 2005, Society for Endocrinology, 2016, Zhou, 2009, Jain, 2010, Cloherty, 2012, Taketomo, 2014*)

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN M SHARRETTS
05/26/2017

MARINA ZEMSKOVA
05/26/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 208418 **Applicant: Fresenius Kabi** **Stamp Date: 05/16/2016**

Drug Name: Calcium gluconate injection USP 10% **NDA/BLA Type: Type 7 – Drug already marketed without approved NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	The Applicant currently markets Calcium gluconate injection, USP 10% as an unapproved drug, and intends to rely on data in the published literature and medical textbooks to support approval.
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?		X		The Applicant did not conduct any bridging studies.
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	The Applicant is

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	Content Parameter	Yes	No	NA	Comment
					relying on characterization of the pharmacokinetics and pharmacodynamics in the published literature.
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)?			X	The applicant is relying on dosing ranges described in the published literature and medical textbooks.
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	The Applicant is relying on data from the published literature, including several small randomized, controlled trials of subjects with hypocalcemia.
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			The Applicant described the planned submission in a pre-IND meeting. The Division agreed with the general proposed approach.
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The Applicant appears to have addressed the deficiencies the Division identified in the preliminary comments.
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			The Division recommended that the Applicant search pediatric databases to obtain additional safety data to support the referenced literature in the 1 month to 17 years pediatric population.
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

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	Content Parameter	Yes	No	NA	Comment
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			Acceptability of the submitted PLLR data is a review issue.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Whether foreign data in the published literature submitted by the Applicant is

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					applicable to the U.S. population and practice of medicine is a review issue.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	The Applicant did not conduct any clinical studies.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
37.	Are all datasets to support the critical safety analyses available and complete?			X	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	The Applicant did not conduct any clinical studies
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?			X	The Applicant did not conduct any studies
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	The Applicant did not conduct any studies

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Provide additional data to support safety in the pediatric (1 month to 17 years population). In general, the submitted safety database appears to be acceptable for the adult and neonatal (less than one month) populations. During review of the initial Pediatric Study Plan, we recommended that you submit all available data from published literature and pediatric electronic databases to support the safe and effective use of calcium gluconate across the entire pediatric age range. The published literature and FAERS search you submitted do not appear to be sufficient. We recommend that you perform additional searches in pediatric electronic databases to support safety in the pediatric (1 month to 17 years) population and submit your findings to the application.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer	Date
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN M SHARRETTS
07/18/2016

MARINA ZEMSKOVA
07/19/2016