

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208418Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	6/9/2017
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208418
Supplement#	
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(s)	(b) (4)
Recommended:	Approval

1. Introduction

On May 16, 2016 Fresenius Kabi submitted a New Drug Application (NDA) for Calcium Gluconate Injection under Section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act.

The applicant proposed the following indication:

Calcium Gluconate Injection is indicated for (b) (4)

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 (b) (4)

2. Background

Hypocalcemia can present as an asymptomatic laboratory finding or as a severe, life-threatening medical condition. The common manifestations of hypocalcemia are symptoms associated with neuromuscular irritability (paresthesia, myalgia, bronchospasm, laryngospasm) and cardiac manifestations (QT-interval prolongation, ECG changes.). In its most severe presentation, hypocalcemia may result in seizures, cardiac arrhythmias, altered mental status and cardiac arrest. The severity of clinical manifestations depends on the calcium levels: the

most severe and life-threatening symptoms are usually observed at very low serum calcium levels < 7.8 mg/dl (or ionized calcium levels < 2.5 mg/dl). However, the severity of symptoms also depends on other factors including the rate of decrease in serum calcium levels, pre-existing health conditions, cause of hypocalcemia, etc. Thus, patients with acute hypocalcemia may be occasionally symptomatic at calcium levels > 7.8 mg/dl.

Calcium is one of the most important electrolyte and plays an essential role in many intracellular and extracellular processes in the human body. Calcium regulates hormone secretion, muscle contraction, coagulation processes, membrane stability, and several other metabolic processes. Forty percent of circulating calcium is bound to proteins and about 50% is ionized. Ionized calcium is the metabolically active form of calcium.

The major regulators of calcium homeostasis are parathyroid hormone, vitamin D, and calcium itself. When the regulatory pathways that maintain calcium levels are disrupted, hypocalcemia can occur. Disruption of regulatory pathways can be the result of iatrogenic complications (surgical removal of parathyroids) or due to underlying disease (genetic absence of parathyroids, resistance to PTH, severe vitamin D deficiency or resistance, rapid clearance of calcium from circulation due to pancreatitis). Risk of hypocalcemia may be transient, if the underlying cause is correctable (e.g., vitamin D deficiency), or chronic if the underlying condition is not correctable (e.g., a genetic disorder or surgical removal of the parathyroid glands). Hypocalcemia is common in hospital settings and can affect up to 85% of patients in intensive care units¹.

Hypocalcemia may occur in all age groups, including neonates. Neonatal hypocalcemia occurs most often in preterm neonates and in neonates born to mothers with diabetes or hyperparathyroidism. Neonatal hypocalcemia may be due to the immaturity of parathyroid glands, suppressed iPTH levels by high maternal circulating calcium levels or congenital agenesis or dysgenesis of the parathyroid glands (e.g., DiGeorge syndrome). Hypocalcemic neonates may have hypotonia, tachycardia, tachypnea, apnea, poor feeding, jitteriness, tetany, and/or seizures.

Hypocalcemia cannot remit spontaneously if the underlying cause is not treated (e.g., repletion of vitamin D stores, etc.); thus, until the underlying condition has been adequately treated, treatment with calcium is required to correct calcium levels and hypocalcemia-associated symptoms and signs. The severity and chronicity of the hypocalcemia dictate the dose and route of administration of calcium treatment. Because acute, severe, hypocalcemia may manifest as life-threatening conditions such as seizures, cardiac arrhythmias, laryngeal spasm, or altered mental status, the American Heart Association (2005)² and other scientific

¹ Cooper MS, Gittoes NJ. Diagnosis and management of hypocalcaemia. *BMJ* 2008; 336(7656):1298-1302

² American Heart Association. Part 10.1: Life-Threatening Electrolyte Abnormalities. 2005

societies³⁴⁵ recommend rapid correction of calcium levels with intravenous calcium infusion. In contrast, chronic, mild, hypocalcemia may can be treated with oral calcium replacement and vitamin D metabolites.

Intravenous calcium is available in two salt forms, chloride and gluconate:

- 10% Calcium Chloride Injection, USP (NDA 02117; Hospira, approved in 2000) is the only approved calcium formulation for the treatment of hypocalcemia “in those conditions requiring a prompt increase in plasma calcium levels”. Administration of calcium chloride is irritating to peripheral veins and can cause peripheral vasodilation and a cutaneous burning sensation; it may also cause tissue necrosis when injected into tissues or if extravasation occurs.
- Calcium Gluconate Injection, USP 10% (Fresenius Kabi US, American Regent, Inc.) is a marketed, unapproved drug on the US market. It is widely used in hospital settings for the treatment of conditions arising from calcium deficiencies including tetany, hypocalcemia due to hypoparathyroidism, and hypocalcemia due to rapid growth or pregnancy. Of note, calcium gluconate injection, USP 10% is also used in non-hypocalcemic conditions (e.g., lead poisoning); however, these uses are outside the scope of this application and will not be further discussed.

The Sponsor seeks approval for Calcium Gluconate Injection for [REDACTED] (b) (4)
[REDACTED] The Sponsor believes that i.v. administration of calcium gluconate rapidly corrects calcium levels, and thus, improves severe symptoms associated with hypocalcaemia (such as seizures, cardiac arrhythmias, etc.).

Regulatory History

Precedent Case example

As stated above, 10% Calcium Chloride Injection, USP is the only approved calcium formulation for the treatment of hypocalcemia “in those conditions requiring a prompt increase in plasma calcium levels” (NDA 02117; Hospira, approved in 2000). The efficacy and safety

³ The American Academy of Pediatrics. Drugs for pediatric emergencies. Committee on Drugs, Committee on Drugs, 1996 to 1997, Liaison Representatives, and AAP Section Liaisons. *Pediatrics* 1998; 101(1):E13.

⁴ The American Academy of Pediatrics. Drugs for pediatric emergencies. Committee on Drugs, Committee on Drugs, 1996 to 1997, Liaison Representatives, and AAP Section Liaisons. *Pediatrics* 1998; 101(1):E13.

⁵ Turner J, Gittoes N, Selby P. Society for Endocrinology Emergency Endocrine Guidance: Emergency management of acute hypocalcaemia in adult patients. *Endocr Connect* 2016; 5(5): G7-G8.

of Calcium chloride was established based on data from the published literature; no clinical studies were conducted.

Calcium Gluconate Regulatory History

No nonclinical or clinical studies with Calcium Gluconate were conducted by the Sponsor to support the proposed indication and no IND for calcium gluconate for the (b) (4) has been submitted to the Agency.

The following are the major regulatory interactions that took place between DMEP and the Sponsor regarding the Calcium Gluconate development program for the (b) (4)

Pre-IND meeting (8/19/ 2011)

The Agency provided the overall recommendations regarding the requirements for submission of a literature based NDA under section 505(b) (2) of the FDCA. The Agency also requested the further clarifications regarding the proposed doses, risks associated with extravasation hypercalcemia, etc. Lastly, the Agency also indicated that the proposed indication, i.e. (b) (4) was reasonable, however the exact language for the indication could not be agreed at that time until the specific information and strength of the evidence will be reviewed.

NDA submission (5/ 16/2016)

User fee goal is extended to 6/16/2017 (Division's Letter from 2/23/2017)

The Division extended the user fee goal date to 6/ 16/2017 due to the submission of a major amendment to the application addressing the CMC issues.

3. CMC/Device

The CMC reviewers recommend approval of this application (refer to Dr. Tran's executive summary). There are no outstanding issues that preclude approval. All facilities inspections have been completed and the Office of Pharmaceutical Quality and Office of Compliance has determined these facilities are acceptable (refer to review in Panorama dated 5/15/2017).

The drug substance, calcium gluconate monohydrate, is a white crystalline powder, sparingly soluble in water, freely soluble in boiling water, insoluble in almost all organic solvents. The CMC review indicates that the Sponsor refers to DMF (b) (4) for all the CMC information on the API. The specification is based on the USP monograph with the addition of Residual Solvents, Bioburden, and Bacterial Endotoxins. DMF (b) (4) was reviewed recently (on (b) (4)) by the Agency and was found to be acceptable.

The drug product, Calcium Gluconate Injection, is a sterile, preservative-free solution to be diluted with 5% Dextrose Injection, 0.9% Sodium Chloride Injection, (b) (4)

(b) (4) Excipients are 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. Calcium saccharate tetrahydrate (b) (4) (b) (4) is acceptable per current USP monograph for Calcium Gluconate Injection.

The presentation is 10 ml, 50 ml and 100 ml vials. Each 1 mL provides 100 mg of **calcium salt** (as 94 mg of calcium gluconate and 4.5 mg of calcium saccharate tetrahydrate) equivalent to 9.3 mg of **elemental calcium**.

The container closure system, a (b) (4) vial with a (b) (4) stopper, was found to be adequate. CMC reviewer concluded that adequate information was provided on extractable/leachables from the product-contact packaging components. Pharmacology-toxicology reviewers also did not identify any safety concerns with container leachables (refer to Nonclinical Pharmacology/Toxicology section below).

The drug product specifications were found to be adequate and were based on the USP monograph, with the addition of description of aluminum, container/closure integrity, and degradation. The specification includes a limit of 400 parts per billion for aluminum, which would result in aluminum levels below the safety threshold of less than 5 mcg/kg/day for the populations at risk (pediatric populations and patients with impaired renal function).

An expiry of 24 months was granted when stored at room temperature. The product lacks an antimicrobial preservative; therefore, the in-use period of the to-be-administered diluted product is limited to 4 hours.

This applicant relies on the published literature to establish the safety and effectiveness of their product and submitted a waiver from having to conduct in vivo bioavailability/bioequivalence studies to bridge the proposed drug product to the products used in the published literature. The biopharmaceutics reviewer, Dr. An-Chi Lu, concluded that submitted data in this NDA supports bridging between the proposed drug product and the products used in the published literature. The reviewer concluded that “the proposed formulation will be administered as an intravenous solution and does not contain any ingredients that are expected to affect the bioavailability of the proposed product”.

4. Nonclinical Pharmacology/Toxicology

The Sponsor did not conduct nonclinical studies with Calcium Gluconate Injection. Instead, the nonclinical data presented in this application summarizes information from published literature. There are no pharmacology/toxicology approvability issues for this application (refer to the review in DARRTS from 5/11/2017, for details of the nonclinical program).

According to Dr. Arulananam K. Thilagar, calcium gluconate metabolism is limited to the gluconate component of the salt, as ionized calcium itself does not undergo direct metabolism. Gluconate is a normal product of glucose metabolism. The daily production of gluconate from endogenous sources is estimated to be about 450 mg for a 60 kg person and does not exceed the amount of glucuronate from the proposed (b) (4) of Calcium Gluconate Injection for the (b) (4). The general toxicological concern for gluconate is very low, because it is an endogenous compound.

The toxicology profile of Calcium Gluconate is mainly attributable to increase in serum calcium above the normal range. The primary toxicities associated with hypercalcemia in laboratory animals are soft tissue mineralization (especially in the kidneys), hypercalciuria, nephropathy, weight loss, altered bone metabolism, decreased clotting time, abnormal heart rhythms and neurologic effects (altered behavior).

Calcium Gluconate Injection has not been evaluated in lifetime rodent carcinogenicity studies. However, calcium gluconate has been shown to be negative in mutagenicity assays conducted in bacteria and yeast. The proposed acute clinical use of Calcium Gluconate is not considered to carry a genotoxic and carcinogenic risks.

No animal reproduction studies were conducted with Calcium Gluconate Injection. However, reviewer indicated that use of Calcium Gluconate Injection during pregnancy is considered to carry a low risk for reproduction toxicity in the absence of hypercalcemia.

Calcium Gluconate Injection contains an excipient, calcium saccharate, as a (b) (4) and co-active pharmaceutical ingredient. The reviewer indicated that no significant toxicological concern for calcium saccharate was identified.

No container leachables above the threshold of toxicological concern were identified.

The impurity of toxicological concern identified for Calcium Gluconate Injection (based on the proposed product specifications submitted with the NDA) was aluminum. Aluminum may be potentially toxic to the CNS and bone, especially in patients with poor renal function, including neonates. The reviewers confirmed that the limit of aluminum in the most recent finished product specification is 400 mcg/ml. They concluded that the aluminum limit of 400

mcg/L is acceptable, since at the maximum recommended doses of Calcium Gluconate Injection, the daily aluminum exposure will be less than 5 mcg/kg/day. However, the reviewers recommend to include the information regarding the content of aluminum in Calcium Gluconate Injection in Warning and Precaution section (Section 5) of the label (as per CFR 201.323).

5. Clinical Pharmacology/Biopharmaceutics

Drs. Renu Singh and Jayabharathi Vaidyanathan note that there are no clinical pharmacology approvability issues for this application. For detailed discussion, please refer to their Clinical Pharmacology review in DARRTS (2/11/2017).

The sponsor has not conducted any clinical pharmacology studies with Calcium Gluconate in the proposed doses; the clinical pharmacology information is based on published literature.

Pharmacokinetic

Based on Dr. Singh's review of PK information from the submitted literature, PK properties of Calcium Gluconate Injection are:

Absorption: Bioavailability is 100% since this is an IV administration.

Distribution: Calcium in the body is distributed mainly in skeleton (99%), and 1% of the total body calcium is distributed within the extracellular fluids and soft tissues. About the 50% of total serum calcium is in the ionized form and represents the biologically active part. 8% to 10% serum calcium is bound to organic and inorganic acids and approximately 40% is protein-bound.

Metabolism: Calcium itself does not undergo direct metabolism. Calcium gluconate dissociates to provide ionized calcium in plasma. Both ionized calcium and gluconate are normal constituents of the body fluids.

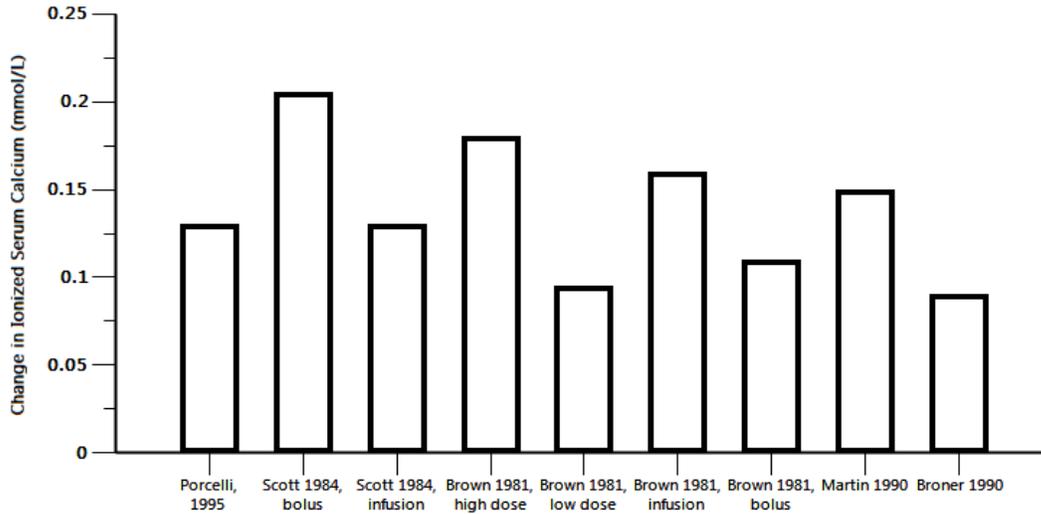
Pharmacodynamics

The PD properties of calcium gluconate are well known. Clinical Pharmacology reviewers reviewed the proposed doses of Calcium Gluconate and found these doses and proposed dosing regimens to be acceptable for all age groups and are supported by sufficient evidence from the published literature.

Briefly, increase in serum total calcium levels and/or ionized calcium levels following administration of calcium gluconate via i.v bolus or continuous infusion was observed across all published randomized control trials; these trials included adult and pediatric patients with

hypocalcemia induced by different causes (trauma, postsurgical hypocalcemia, critically ill patients, etc.) (Figure 1).

Figure 1. Change in ionized serum calcium from baseline in randomized control trials evaluating calcium gluconate in pediatric and adult patients



Source: Clinical Pharmacology review, figure 1.

Some studies demonstrated that there was a dose-dependent PK^{6 7}, while the other studies demonstrated the similar increase in calcium levels following the administration of different doses. Dr. Singh indicated that calcium levels were measured at different time points in these studies complicating the interpretability of the results. Overall, Dr. Singh concluded that there was a limited evidence of dose-response or dose proportionality obtained from these studies.

Drug-Drug Interaction (DDI)

The Sponsor proposed to include information regarding Calcium Gluconate Injection interactions with cardiac glycosides, (b) (4), ceftriaxone, Vitamin D, calcium channel blockers, (b) (4) diuretics, phosphate and bicarbonate in Section 7 of the label. The reviewers found the proposed language to be acceptable for the majority of the proposed DDIs. However, the reviewers recommended that information regarding DDI with (b) (4) be revised, since the interaction was related to the absorption and “was deemed not applicable in an IV settings”. The reviewers also recommended to include the information

⁶ Dickerson RN, Morgan LM, Croce MA, Minard G, Brown RO. Dose-dependent characteristics of intravenous calcium therapy for hypocalcemic critically ill trauma patients receiving specialized nutritional support. *Nutrition* 2007a; 23(1):9-15

⁷ Brown DR, Steranka BH, Taylor FH. Treatment of early-onset neonatal hypocalcemia. Effects on serum calcium and ionized calcium. *Am J Dis Child* 1981; 135(1):24-28.

regarding the risk of hypercalcemia associated with concomitant administration of Calcium Gluconate Injection with other drugs that raise the calcium levels (e.g. Vitamin D, (b) (4) diuretics) in Section 5 (Warnings and Precautions section). I disagree with the reviewers' recommendation: hypercalcemia is likely to be rare and mild in the intended use (correction of acute/severe hypocalcemia) if it occurs at all, folks with normal renal function would likely clear excess calcium. It is reasonable to remind prescribers that calcium levels may rise more if patients are taking drugs that are known to raise calcium levels in the drug-drug interaction of the label (Section 7).

Intrinsic Factors that could Influence Exposure and Activity

The clinical pharmacology reviewers indicated that, based on the information from the published literature, no dose adjustment is required for the geriatric population and population of patients with hepatic or renal impairment. On first principles, we expect that less calcium will be needed to correct hypocalcemia in patients who cannot clear calcium (i.e., patients with end stage renal disease). The drug is titrated to effect and the desired effect may be reached with less calcium in these patients. I concur that no adjustment to the initial dose of drug is needed in these patients given the fact that the dose is titrated to effect and the calcium levels are monitored during therapy.

6. Clinical Microbiology

The microbiology review was completed as part of the product quality review. Quality microbiology data was reviewed by Drs. Yuansha Chen and Neal J. Sweeney on 1/13/2017. No concerns were identified by the reviewers.

7. Clinical/Statistical- Efficacy

The data to support the efficacy of Calcium Gluconate for the treatment of acute symptomatic hypocalcemia is derived exclusively from the published literature. The submitted published literature includes randomized controlled and non-randomized prospective studies, retrospective studies, case studies, review articles, professional scientific society guidelines and medical textbook recommendations on the treatment of acute hypocalcemia.

Dr. Sharretts reviewed the 48 publications that the applicant submitted to support a determination of efficacy for Calcium Gluconate Injection (b) (4). Dr. Sharretts noted that the majority of articles used serum calcium or ionized calcium values to evaluate efficacy and that some studies also reported on changes to patient symptoms and/or signs (vital signs, ECG changes, etc.). I agree with Dr. Sharrett that the measurement of serum calcium before and after infusion of calcium gluconate is a face-valid outcome measure to establish the clinical benefit of this product, since clinical symptoms and signs of hypocalcemia are closely associated with serum calcium levels and cannot remit

spontaneously without calcium correction; thus, “the effect of calcium gluconate infusion on serum calcium levels (and thus on the improvement of hypocalcemic symptoms) is self-evident”.

Overall, the published literature provides the necessary evidence across all age groups (adult, children, neonates) to establish that intravenous calcium gluconate infusion effectively increases calcium levels in patients with hypocalcemia caused by different etiologies (critical illness, post-parathyroidectomy, neonates with transient hypocalcemia, etc.). The magnitude of increase in calcium levels was noted to vary among publications as a function of dose, rate of infusion and timing of calcium level assessment. Table 1 summarizes doses and changes in serum ionized calcium levels from a selected number of publications submitted.

Table 1: Increase in Serum Ionized Calcium by Dose and Age Group

Source	Number of Subjects	Total Daily Dose: Calcium gluconate	Ionized Calcium Increase (mg/dL)	Time of assessment
Adult Patients				
<i>Dickerson 2005</i>	8	1000 mg	0.32	24 hours
<i>Steele 2013</i>	539	1000 mg	0.20-0.72	24 hours
<i>Dickerson 2007a</i>	10	2000 mg	0.44	24 hours
<i>Dickerson 2005</i>	21	2000 mg	0.64	24 hours
<i>Martin 1990</i>	7	1800-3000 mg	0.60	10 minutes
<i>Dickerson 2007a</i>	15	4000 mg	0.96	24 hours
<i>Dickerson 2007b</i>	20	4000 mg	1.04	24 hours
Pediatric Patients Ages > 1 month to < 17 years				
<i>Broner 1984</i>	20	29 mg/kg	0.37	30 minutes
<i>Kossoff 2002</i>	1	75 mg/kg	1.72	3 days
<i>Helikson 1997</i>	1	140 mg/kg	1.0	6 hours
<i>Hebbar 2006</i>	1	250 mg/kg	1.5	8 hours
<i>Geffner 1980</i>	1	300 mg/kg	4.0*	18 hours
<i>Raffaella 2009</i>	1	300 mg/kg	3.6*	9 days
Neonatal Patients < 1 month				
<i>Porcelli 1995</i>	22	100 mg/kg	0.5	3-6 hours
<i>Bifano 1989</i>	10	200 mg/kg	1.1	1 hour
<i>Venkataraman 1985b</i>	8	200 mg/kg	0.4	8 hours
<i>Brown 1982</i>	24	200 mg/kg	0.4	5 hours
<i>Scott 1984</i>	9	400 mg/kg	0.3	24 hours
<i>Brown 1981</i>	18	400 mg/kg	0.39	24 hours
<i>Brown 1981</i>	18	600 mg/kg	0.72	24 hours
<i>Scott 1984</i>	9	800 mg/kg	0.72	24 hours
*Total serum calcium				

Source: Clinical Review, p. 44, table 10.

Below, I will briefly summarize the data that support the establishment of efficacy of calcium gluconate, at the proposed doses, for each age group. Refer to Dr. Sharretts' review for a detailed discussion of all publications submitted to support the efficacy of calcium gluconate. Please note that all doses of calcium gluconate in this review are given in mg/kg of calcium gluconate.

Efficacy of calcium gluconate in adults with hypocalcemia

The data to support the efficacy of calcium gluconate in adults is obtained from 13 published articles evaluating calcium gluconate in approximately 688 adult patients with hypocalcemia. Data in the publications (including 2 randomized controlled studies, 2 single-arm, prospective studies and several reviews and guidelines) consistently demonstrate that administration of calcium gluconate as a single bolus, or as repeated boluses every 6 hours in doses 1000-2000 mg (and up to 4000 mg) or as a continuous infusion in doses up to 1000 mg/hr (total dose up to 216000 mg/day at average rate 17 mg/kg/hr) effectively raise serum calcium levels from baseline (by 0.2- 1.04 mg/dl of ionized calcium) in patients with hypocalcemia.

As stated previously, the magnitude of the ionized calcium change varied predictably based on the dose administered, the rate of administration and timing of calcium assessment (refer to Table 1 above). Bolus doses in all studies were administered at rates of approximately 100-200 mg per min (e.g., 1000-2000 mg delivered over 10 minutes) to decrease the risk of cardiac arrhythmias associated with rapid calcium infusion.

The doses studied in the publications are consistent with dosing adopted by professional societies. For the treatment of acute severe hypocalcemia, the 2005 American Heart Association guidelines⁸ recommend administering 1000 to 2000 mg of **calcium gluconate**⁹ as a bolus over 10 minutes (i.e., 10-20 ml of a 10% calcium gluconate solution). For very severe hypocalcemia the initial dose can be followed by either; repeating the bolus every 6 hours until calcium normalizes and symptoms resolve or by initiating a continuous infusion of a calcium gluconate solution containing 5.8 to 7.7 mg of **calcium gluconate** per mL¹⁰. The guidelines recommend an infusion rate of 5.4 to 21.5 mg of **calcium gluconate** per kg per hour until calcium levels normalize. During correction serum calcium levels are monitored every 3 to 4 hours. The doses and dosing regimens recommended by the Society for Endocrinology (2016) are similar to the AHA recommendations (refer to Dr. Sharretts' review).

⁸ American Heart Association. Part 10.1: Life-Threatening Electrolyte Abnormalities. 2005

⁹ **Note:** Calcium dosing is sometimes represented as amount of "elemental" calcium. The amount of elemental calcium varies based on the product formulation. The bold formatting denotes that the dose refers to the product itself and not elemental calcium.

¹⁰ i.e., 58 to 77 ml (i.e., 5800 to 7700 mg) of 10% of calcium solution diluted in 1 L of saline or 5% dextrose

Thus, the applicant's proposed doses of **calcium gluconate**, 1000 to 2000 mg as a single bolus followed by repeated boluses every 6 hours or by a continuous infusion at a rate of 5.4- 21.5 mg per kg per hour if needed are: within the range studied, consistent with doses recommended by professional societies, and are doses currently used in the acute care setting to correct severe hypocalcemia. These doses are expected to increase calcium levels safely and effectively in patients with various degree of acute hypocalcemia.

Efficacy of calcium gluconate in neonates (< 1 month old)

Dosing recommendations for neonatal patients are derived from 4 randomized-controlled trials, 3 single arm trials and several case-report studies evaluating the effect of calcium gluconate on calcium levels and associated symptoms in approximately 187 neonates with hypocalcemia. The results of the four randomized-controlled studies and several single arm prospective studies (refer to Dr. Sharretts's review for the list of references) demonstrated that a single weight-based bolus dose of 100 to 200 mg/kg of **calcium gluconate** successfully increases serum ionized calcium by 0.1-0.25 mmol/l for up to 8 hours.

Bolus dosing can also be followed by continuous infusion. As Dr. Sharretts notes, the Sponsor's proposed a continuous infusion dose [i.e., (b) (4) of **calcium gluconate** ((b) (4) mg/kg/hr)] is on the low end of doses supported by data in the published literature. The data from the published studies demonstrate that a continuous infusion of 400 to 800 mg/kg/day of **calcium gluconate** (i.e., 17-33 mg/kg/hr) increases serum ionized calcium by 0.08-0.18 mmol/l over 24 hours in neonatal patients with hypocalcemia. These doses are also in line with doses recommended by pediatric professional society guidelines¹¹ and pediatric textbooks¹² for the treatment of acute hypocalcemia in this population (refer to Dr. Sharretts's review).

Thus, the overall data supports the following **calcium gluconate** doses in neonates: initial bolus of 100-200 mg/kg followed by either repeated boluses of 100-200 mg/kg every 6 hours or by continuous infusion of 17-33 mg/kg/hr.

Efficacy of calcium gluconate in pediatric patients > 1 months old

The data to support the efficacy of **calcium gluconate** in children > 1 month old was obtained from 17 published articles: 1 randomized controlled study, 1 non-randomized, prospective

¹¹ The American Academy of Pediatrics. Drugs for pediatric emergencies. Committee on Drugs, Committee on Drugs, 1996 to 1997, Liaison Representatives, and AAP Section Liaisons. *Pediatrics* 1998; 101(1):E13.

¹² Taketomo C, Hodding J, Kraus D. Pediatric & Neonatal Dosage Handbook. 21 ed. Hudson, OH: Wolters Kluwer, 2014.

¹³ Cloherty J, Eichenwald E, Hansen A. Manual of Neonatal Care. Lippincott Williams & Wilkins, 2012.

study and several case reports evaluating calcium gluconate in a total of 46 patients with acute hypocalcemia and from several review articles, pediatric guidelines and textbooks.

The results of a randomized trial ¹⁴ demonstrated that a bolus dose of 29 mg/kg of **calcium gluconate** rapidly increased serum ionized calcium in 20 pediatric patients with baseline hypocalcemia. Several case reports and review articles demonstrated that administration of bolus doses of 55 to 90 mg/kg of **calcium gluconate** or continuous infusion of **calcium gluconate** in doses up to 800 mg/kg/day (33 mg/kg/hr) increased serum calcium levels by up to 1.5 mg/dl depending on dose, rate of infusion and time of calcium measurements after the infusion (refer to Dr. Sharretts's review, Tables 1, 10 and 11). However, Dr. Sharretts noted that the upper end of the range of doses for continuous infusion are derived from studies in neonates and are not applicable to the older age group. Some articles also reported the resolution of tetany, respiratory failure and "improvement in symptoms" (symptoms are not specified).

The American Academy of Pediatrics¹⁵ recommends using single bolus doses of up to 60 mg/kg and a pediatric textbook (Pediatric and Neonatal Dosage Handbook) recommends using a continuous infusion of calcium gluconate at rates of 8 to 13 mg/kg/hr (i.e., 200-300 mg/kg/day) in children with acute hypocalcemia.

Thus, the proposed **calcium gluconate** doses in children > 1 month old of 29-60 mg/kg (bolus or repeated boluses administered every 6 hours) and continuous infusion of 8-^(b)₍₄₎ mg/kg/hr, are within the range of effective doses used in published studies, doses currently used in practice, doses recommended in pediatric textbooks¹⁶ ¹⁷ and doses recommended by professional society guidelines¹³.

In conclusion, I agree with Dr. Sharretts that **calcium gluconate** in the proposed doses and dosing regimens effectively increases calcium levels across all age group in patients with symptomatic hypocalcemia of various etiologies (critical illness, parathyroidectomy, drug-induced, etc.). The findings from published studies are consistent with current recommendations on treatment of acute hypocalcemia by professional guidelines and medical textbooks.

¹⁴Broner CW, Stidham GL, Westenkirchner DF, Watson DC. A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children. *J Pediatr* 1990; 117(6):986-989.

¹⁵ The American Academy of Pediatrics. Drugs for pediatric emergencies. Committee on Drugs, Committee on Drugs, 1996 to 1997, Liaison Representatives, and AAP Section Liaisons. *Pediatrics* 1998; 101(1):E13.

¹⁶ Taketomo C, Hodding J, Kraus D. Pediatric & Neonatal Dosage Handbook. 21 ed. Hudson, OH: Wolters Kluwer, 2014.

¹⁷ Corporate Authors. Drug Facts and Comparisons 2015. Clinical Drug Information, LLC, 2014.

I recommend that for continuous infusion, doses of **calcium gluconate** be expressed as mg/kg/hour rather than (b) (4) (as currently proposed by the Sponsor). Overall, the risk of overdosing and hypercalcemia associated with excessive daily doses is extremely low since calcium levels are frequently monitored during the infusion and the infusion is stopped once the calcium levels are above symptom threshold and/or the symptoms have improved. In addition, expressing the dose in mg/kg/hour will mitigate against medication errors (i.e., mistakenly confusing the daily dose for an hourly dose) and risks associated with overdose of the product.

8. Safety

Injectable calcium gluconate has a long history of use in different clinical situations. It is currently widely used for the treatment of symptoms associated with acute hypocalcemia (seizures, cardiac arrhythmias, etc.) in hospital settings and is an essential emergency drug used universally. Clinicians are familiar with the safety profile of injectable calcium gluconate given the well understood calcium physiology and the long-term experience with use of **calcium gluconate** in clinical practice. The potential risks associated with intravenous administration of calcium gluconate are mainly related to its pharmacology (e.g., signs and symptoms of hypercalcemia) and to its effect on tissues if it escapes the circulation (e.g., calcium-induced tissue inflammation and necrosis due to extravasation). Gluconate is a normal byproduct of glucose metabolism; thus, no adverse events are expected from the gluconate component of the drug. Calcium gluconate is considered to be less of a local irritant (e.g., better tolerated) and better tolerated than calcium chloride and is preferred for this reason over calcium chloride.

The Sponsor included 150 published studies in this NDA to support the safety of Calcium Gluconate Injection for the proposed indication. These publications were reviewed by Dr. Sharretts and discussed in detail in his clinical review (refer to his review for details). Dr. Sharretts concludes that the safety profile of Calcium Gluconate Injection is similar to the safety profile of Calcium Chloride, a formulation currently approved for the treatment of acute hypocalcemia. No new or unexpected safety signals for calcium gluconate were identified in the literature. However, Dr. Sharretts also indicated that the estimation of the frequency of the AEs was complicated due to the limitations of published data (e.g. publications present limited information on safety or on how safety was evaluated during the study). Lastly, he also reviewed the adverse events associated with calcium gluconate identified in FAERS and concluded that these were consistent with those reported in published literature.

Briefly, the most serious adverse events associated with i.v. administration of calcium gluconate are cardiac arrhythmias, bradycardia and cardiac arrest. These AEs are associated with rapid injection of a concentrated solution of calcium gluconate. These AEs are

preventable by administration of a diluted calcium solution at slow rate and by cardiac monitoring during calcium administration.

The other more common and less severe complications associated with use of calcium gluconate are injection site reactions, soft tissue inflammation and skin necrosis and calcinosis cutis that are most frequently due to extravasation of calcium gluconate. Dr. Sharretts indicated that calcinosis cutis may occur in the absence of extravasation and is most likely due to a local elevation of calcium levels since most of these adverse events were observed at high doses. All adverse reactions typically resolve with supportive care. The majority of publications, guidelines and medical textbooks recommend dilution of calcium gluconate prior to administration and administration of the drug through large veins to decrease the risks of extravasation, tissue inflammation and necrosis.

Lastly, rapid or prolonged infusion of calcium in large doses may result in hypercalcemia with clinical consequences (myocardial depression, hypertension, cardiac arrhythmias, etc.). Short-term use of the product within the appropriate dosing range, simultaneous cardiac monitoring and close monitoring of calcium levels during the infusion mitigates these effects.

In the Adverse Reactions Section (section 6) of the label, the Sponsor also included adverse events associated with [REDACTED] (b) (4). However, Dr. Sharretts indicated that these AEs are not relevant to short-term parenteral treatment of acute symptomatic hypocalcemia and recommended that these AEs be removed from the label.

Dr. Sharretts concluded that the application provided sufficient data on the safety profile of the drug to be included in the label. Overall, calcium physiology is well understood, there has been a long clinical experience with the use injectable calcium gluconate in the care setting, and health care providers are familiar with the well-characterized side effect profile associated with calcium gluconate for the intended use. More importantly, the risks associated with the use of calcium gluconate can be mitigated through product labeling, appropriate dose selection and administration technique, close monitoring and discontinuation of the drug if need be.

Finally, I am in agreement with Dr. Sharretts that the benefits for the dosing regimen proposed, across each age group, outweighs the risks.

9. Advisory Committee Meeting

No AC meeting was held.

10. Pediatrics

An agreed Initial Pediatric Study Plan (iPSP) was issued by the Division on April 13, 2016. During the review of data submitted in this NDA, the Division requested the Sponsor to provide additional information to support the use of the product in pediatric patients > 1 month old. The Sponsor submitted the required data on 2/10/2017. This additional safety information was reviewed by Dr. Sharretts and DPMH reviewers and was found to be sufficient to support the intended use of calcium gluconate across all pediatric age groups.

A proposed pediatric study plan and the label containing the pediatric information submitted in this NDA were reviewed and discussed by the Pediatric Review Committee on 4/20/2017.

11. Other Relevant Regulatory Issues

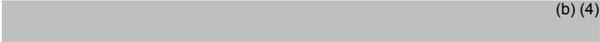
None

12. Labeling

The label was reviewed by Division of Pediatric and Maternal Health (refer to reviews in DARRTS from 5/11/2017 and 5/14/2017) and by Division of Medication Error Prevention and Analysis (DMEPA) ((refer to review in DARRTS from 3/30/2017)

The following major recommended changes to the label were made:

- The indication should be restricted to adult and pediatric patients with acute symptomatic hypocalcemia. (b) (4)

- Limitation of use should be included in the label stating that the drug should not be used for the long -term. The safety profile of Calcium Gluconate associated with long-term use has not been established.
- Dose of calcium gluconate should be expressed in mg of **calcium gluconate** to mitigate against confusion and medication errors. The amount of elemental calcium in mg and meq per ml of the product will be included in the label for reference. This information is used by some prescribers who estimate calcium deficit or dose based on mg or meq of elemental calcium (i.e., a constant across varied calcium formulations).
- The adverse events associated with  (b) (4)
 are not relevant to the intended use and should be removed from Section 6 of the label.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval as benefits of use outweigh the risks

I recommend that the proposed indication for Calcium Gluconate Injection be modified as follows (pending the agreement on the final labeling language):

Treatment of acute symptomatic hypocalcemia



- Risk Benefit Assessment

Benefits:

As indicated in the body of this memorandum, the severity of clinical manifestations of hypocalcemia depends on the calcium levels and on the rate of calcium decrease. Severe acute hypocalcemia is associated with life-threatening medical complications if calcium levels are not promptly corrected. The natural history of acute hypocalcemia is predictable and decreased calcium levels and associated symptoms of hypocalcemia cannot correct spontaneously without either resolution of the underlying cause (an extremely unlikely event for most causes of acute hypocalcemia) or timely exogenous calcium administration. In the setting of acute hypocalcemia, calcium gluconate improves serum calcium levels and signs and symptoms of hypocalcemia. It is thus self-evident that this drug's benefit lies in its ability to prevent the serious life-threatening medical complications caused by severe hypocalcemia.

The data from the submitted published literature demonstrated that Calcium Gluconate Injection at the doses and dosing regimens proposed in the label effectively increase calcium levels in adult and pediatric patients with acute symptomatic hypocalcemia. These data

provide sufficient information to conclude that the benefits of calcium gluconate in patients with acute symptomatic hypocalcemia outweigh the risks associated with the drug. The effect of calcium gluconate on calcium levels in all studies is consistent across all ages and independent of the cause of acute hypocalcemia. The recommended doses are also in line with doses recommended by scientific societies and used in practice for the treatment of acute symptomatic hypocalcemia.

Risks:

The potential risks associated with all injectable calcium formulations are well recognized. The most common adverse reactions associated with calcium gluconate infusion include local irritation, especially when administered via peripheral veins, skin and soft tissue inflammation and necrosis associated with calcium extravasation and calcinosis cutis. Dilution of the drug product, infusion through a secure intravenous line, rotation of intravenous sites and timely discontinuation of the infusion when appropriate mitigates these risks.

The most serious risks associated with parenteral calcium infusion are arrhythmias, myocardial depression, and cardiac arrest associated with rapid infusion and/or hypercalcemia. These risks can be mitigated by decrease rate of infusion and/or by drug discontinuation, by cardiac monitoring and monitoring of calcium levels during calcium gluconate infusion.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

None

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

/s/

MARINA ZEMSKOVA
06/09/2017

JEAN-MARC P GUETTIER
06/09/2017
I concur.