Office of Clinical Pharmacology Review

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Submission Date	05/16/2016
Submission Type	Standard Review
Brand Name	
Generic Name	Calcium gluconate injection, (b) (4)
Dosage Form and Strength	Injection, (b) (4)
Route of Administration	Intravenous
Proposed Indication	(b) (4)
Applicant	Fresenius Kabi USA, LLC
Associated IND	IND 113171
OCP Review Team	*Renu Singh, PhD*
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1. EXECUTIVE SUMMARY

Fresenius Kabi USA seeks approval of calcium gluconate injection, (b) (4) for the (b) (4) via the regulatory 505(b)(2) pathway. The applicant's calcium gluconate injection (b) (4) is a sterile, non-pyrogenic, supersaturated solution of calcium gluconate for intravenous (IV) use only. To support the approval of this 505(b)(2) application, the sponsor intends to rely on information from published literature, clinical societies guidelines and text books of medicine. The supportive information in the published scientific literature for the efficacy of calcium gluconate for IV use includes 6 pivotal studies involving 128 patients with symptomatic/nonsymptomatic hypocalcemia and 62 supportive efficacy studies involving 1311 subjects. For safety analysis, 150 studies involving 3298 subjects were submitted. The proposed product is marketed unapproved for many years and is currently listed in the drug shortage list.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 208418 Clinical Pharmacology data submitted on May 16, 2016 and recommends approval. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Published scientific literature for the efficacy of calcium gluconate for IV use includes 6 pivotal studies involving 128 patients with symptomatic/nonsymptomatic hypocalcemia and 62 supportive efficacy studies involving 1311 subjects.
General dosing instructions	The proposed dosing is acceptable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The proposed dosing is acceptable.
Labeling	See section 2.4 for labeling.
Other (specify)	None

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Calcium gluconate is a mineral supplement of calcium and IV administration of calcium gluconate increases serum ionized calcium level rapidly and effectively. Pharmacokinetics (PK) properties are listed below:

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

Distribution: Calcium in the body is distributed mainly in skeleton (99%). Only 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% to10% serum calcium is bound to organic and inorganic acids (eg. citrate, sulfate and phosphate) and approximately 40% is protein-bound (80% to albumin and 20% to globulins).

Metabolism: Calcium itself does not undergo direct metabolism.

Elimination: Approximately 80% of orally administered calcium is excreted in the feces as insoluble salts; urinary excretion accounts for the remaining 20%.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Dosing recommendations for adults, neonates and pediatrics are shown in Table 1:

Table 1. Summary of dosing recommendations for patients of all ages.

2.2.2 Therapeutic individualization

No dose adjustment is required for geriatric population and population with hepatic or renal impairment.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

Summary of labeling recommendation for different sections are listed below:

- Section 2: The proposed dosing recommendations are acceptable.

- Section 7: Drug-drug interaction (DDI) recommendations with the following drugs were proposed by the sponsor:
  - Cardiac glycosides
  - (b) (4)
  - Ceftriaxone
  - Vitamin D
  - Calcium channel blockers
  - (b) (4)
  - Diuretics
  - Phosphate and bicarbonate
  - (b) (4)
  - (b) (4)

After review, it was concluded that the language proposed for the interactions with cardiac glycosides, ceftriaxone, calcium channel blockers and phosphate/bicarbonate containing solutions were acceptable. DDI information for (b) (4) However, minocycline label states incompatibility with IV calcium gluconate. DDI of relevant tetracycline antibiotics with IV calcium administration will be reflected in the label. Vitamin D, calcitonin, diuretics and impact of IV calcium administration were considered more appropriate to be included in Section 5- Warnings and Precautions.

- Section 8: The dose recommendation for geriatrics, renal and hepatic impaired patients are acceptable.
- Section 12.3: The labeling statements are acceptable.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Calcium gluconate is a mineral supplement of calcium and IV administration of calcium gluconate increases serum ionized calcium level rapidly and effectively. A similar product - calcium chloride from Hospira (NDA 021117) was approved in 2000.

A Pre-IND briefing package was provided by the sponsor on October 6, 2011 in order to seek guidance from the Agency with respect to a proposed 505(b)(2) NDA for the drug product. The Agency provided Pre-IND meeting preliminary comments on November 15, 2011 in which the proposed 505(b)(2) submission pathway was considered acceptable. The Agency requested a clear analysis of all medical text books and published trials regarding dosing of calcium gluconate injection. The requests included evaluation of the need for rapid correction of severe hypocalcemia while avoiding the risk of hypercalcemia; the need for different doses based on the severity of the hypocalcemia; safe infusion rate and the maximum infusion rate; the frequency of monitoring serum calcium levels; dosing adjustment for normalized serum calcium levels or special medical conditions; potential complications and recommendations on treatment to

prevent tissue necrosis. Further, the Agency concurred that no additional PK or pharmacodynamic (PD) clinical studies are required, and information from medical textbooks and medical literature was sufficient to support 505(b)(2) NDA submission of calcium gluconate Injection, (b) (4)

The sponsor submitted an initial pediatric study plan (iPSP) on July 27, 2015. The Agency requested additional justification for the (b) (4) for neonates. The Agency did not agree with the sponsor's original intentions (b) (4) and instead asked for additional literature data to support the safety and efficacy as well as the (b) (4) of the proposed product for pediatric patients. The sponsor submitted an amendment to the PSP on January 18, 2016 in which additional justification on the (b) (4) for neonates as well as a partial waiver request for the larger pediatric age range was provided. However, per FDA feedback, the partial waiver request was abandoned and instead submitted an agreed-iPSP on March 18, 2016 in which the sponsor committed to providing additional data to support the use of calcium gluconate in the pediatric population ages > 1 month to 17 years. The available literature references are now included in this NDA application in Modules 4 and 5 as appropriate.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Hypocalcemia is defined as a serum calcium concentration <8.5 mg/dL (or ionized calcium of <4.2 mg/dL or <1.05 mmol/L). Hypocalcemia may develop with toxic shock syndrome, with abnormalities in serum magnesium, after thyroid surgery, with fluoride poisoning, and with tumor lysis syndrome (rapid cell turnover with resultant hyperkalemia, hyperphosphatemia, and hypocalcemia). Symptoms of hypocalcemia usually occur when ionized levels fall to 2.5 mg/dL. Symptoms include paresthesias of the extremities and face, followed by muscle cramps, carpopedal spasm, stridor, tetany, and seizures.

Mechanism of Action of Calcium Gluconate

Calcium gluconate is a mineral supplement of calcium and IV administration of calcium gluconate increases serum ionized calcium level rapidly and effectively (Bull, 1980; Cote', 1987; Heining, 1984; Martin, 1990). Calcium is required for excitation contraction coupling in muscle, secretion of hormones and neurotransmitters, enzyme activation, cell division, blood coagulation, membrane stability, and bone structure. Calcium is a major regulator coupling receptor activation to intracellular metabolic events and plays an important role in maintaining cellular and organ integrity. Calcium enters the cell via diffusion, slow calcium-channel activation, and sodium-calcium exchange. Uncontrolled increases in free intracellular calcium can activate destructive processes (ie, lipases, proteases, nucleases, free radical generation and prostaglandin release). Free intracellular calcium concentrations are normally maintained within narrow limits through energy requiring processes, which pump calcium out of the cell or into the sarcoplasmic reticulum. Failure of these pumps during ischemia and sepsis leads to increased free intracellular calcium and cellular damage (Zaloga, 1992).

Pharmacokinetics of Calcium Gluconate

Absorption

The sponsor's calcium gluconate injection is proposed to be used intravenously. Therefore, the bioavailability of the proposed drug product is 100%.

Distribution

Body calcium exists in two major compartments in which skeleton accounts for 99% of the total body calcium, and only 1% of the total body calcium is within the extracellular fluids and soft tissues. About 50% of total serum calcium is in the ionized form and represents the biologically active part. A further 8–10% is bounded to organic and inorganic acids (eg. citrate, sulfate, phosphate) and the remaining percentage of serum calcium (~40%) is protein-bound (80% to albumin, 20% to globulin) (Bozzetti, 2009; Zhou, 2009; Kelly, 2013). Ionized calcium is crucial for many biochemical processes including blood coagulation, neuromuscular excitability, cell membrane integrity and function, and cellular enzymatic and secretory activity (Jain, 2010; Zaloga, 1992). Various factors alter the ratio of ionized calcium to bound calcium, but the most important factor is the albumin concentration. Medical conditions can cause a decrease in serum albumin leading to a low total serum calcium level. However, low total serum calcium concentrations are not necessary hypocalcemia, and the serum calcium levels are needed to be assessed in relation to reference albumin concentrations (Cooper, 2008). Acidemia releases calcium from albumin; alkalosis increases binding. A change of 0.1 pH unit may alter the concentration of ionized calcium by 10% without altering the total calcium concentration (Zhou, 2009).

Metabolism

Calcium gluconate is a mineral supplement of calcium. IV administration of calcium gluconate increases serum ionized calcium level rapidly and effectively. 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. The release of ionized calcium from IV administration of calcium gluconate is direct and does not seem to be affected by the first pass through the liver (Bull, 1980; Heining, 1984; Martin, 1990).

Elimination

A study was conducted on 6 hospitalized males, who convalesced from acute self-limited illness. The subjects were infused 1 g of calcium ion as of calcium gluconate salt over a 4 hour period. The results showed that by 1½ and 3½ hour after the beginning of infusion the mean corrected renal clearance for calcium during the calcium gluconate infusion were 4.68 and 7.41 times, respectively, that of before calcium infusion. At 1 hour after the calcium infusion (5 hour after the beginning of infusion), mean calcium renal clearance was 5.89 times that of before calcium infusion (Bernstein, 1962). These data showed an acute relationship between urinary calcium excretion and IV administration of calcium gluconate.

In a study with 14 preterm hypocalcemic neonates (defined by serum calcium concentration < 7.0 mg/dL), subjects were administrated an IV bolus or through an umbilical arterial catheter at a dose of 18 mg/kg of elemental calcium (200 mg/kg calcium gluconate 10%) over a 2-minute

period. The results showed that a significant increase ($p < 0.05$) in urinary excretion of calcium after the infusion of IV calcium gluconate from 0.08 ± 0.01 mg/kg/5 hour for predose to 0.35 ± 0.08 mg/kg/5 hour postdose. However, the authors estimated that only a mean of 1.5% of the infused calcium was excreted in urine (Brown, 1982).

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The supportive information provided by the sponsor for the efficacy of calcium gluconate for IV use includes 6 pivotal studies involving 128 patients (96 neonatal patients and 32 adult patients) with symptomatic/non-symptomatic hypocalcemia and 62 supportive efficacy studies involving 1311 patients (total 68 clinical studies with 1439 patients). A summary of the six pivotal studies is shown in Table 2.

There was a lack of clarity on the formulation used in these studies. Only 1 study (Buchta 2003) reported the use of calcium gluconate manufactured by the sponsor (Table 2). Across the pivotal randomized, placebo or positive controlled studies, IV administration of calcium gluconate increased ionized serum calcium level in all treated groups (Figure 1). This increase in ionized calcium relative to baseline is evident for neonate population (Figure 2) and adult population (Figure 3) across the studies. Note that for pediatric population (>1 month to <17 years) only one study (Broner, 1990) was listed as the pivotal study by the sponsor, hence a cross-study comparison for this population was not performed.

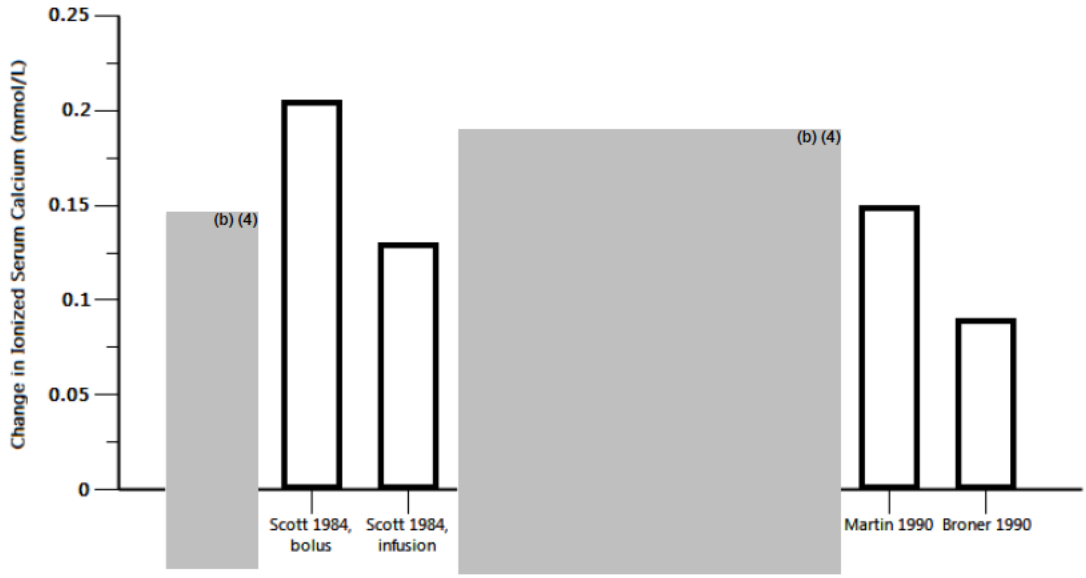
While the neonate studies used different doses ranging from 100 to (b) (4) mg/kg/day almost similar response was observed (Table 2, Figure 2). Although an increase in ionized calcium was observed in all studies, a dose dependent increase was not evident (Figures 1 and 2). Out of the 3 pivotal studies for neonates studies (b) (4). (b) (4) ((b) (4)). (b) (4) (b) (4) . For adult population . Thus, there is limited evidence of dose-response or dose-proportionality (b) (4) While Scott et al. and (b) (4). measured the ionized calcium (b) (4) (b) (4). For adult studies the ionized calcium was measured at (b) (4) and (b) (4) by (b) (4) and (b) (4)., respectively. Additionally the baseline ionized calcium level varied from 0.65 mmol/L to 1.05 mmol/L in the studies (Figures 2 and 3). While these factors limit the interpretation of the studies it is clear that in multiple controlled and non-controlled studies calcium gluconate has been successfully shown to increased serum ionized calcium levels in hypocalcemic neonates, pediatrics and adult patients compared to that of pre-treatment levels. Refer to the clinical review for details on efficacy and safety of this product.

Table 2. Summary of the six pivotal studies.

Source	Population	Dose	Frequency/Route	Formulation
Randomized placebo-controlled studies				
[redacted] (b) (4)				
Scott 1984*, bolus	Neonates (T=9, P=9)	200 mg/kg at 100 mg/min	Bolus, q6h	Ca gluconate
Scott 1984*, infusion	Neonates (T=9, P=9)	400 mg/kg/day	Continuous Infusion	Ca gluconate
[redacted] (b) (4)				
Buchta 2003	Adults (T=25, P=25)	3844 mg at 769mg/hour	Bolus, single dose	Ca gluconate (Fresenius Kabi)
Randomized positive-controlled studies				
Broner, 1990	1 day-17yr (T=20, R=17)	29 mg/kg/dose	Bolus, single dose	Ca gluconate
[redacted] (b) (4)				

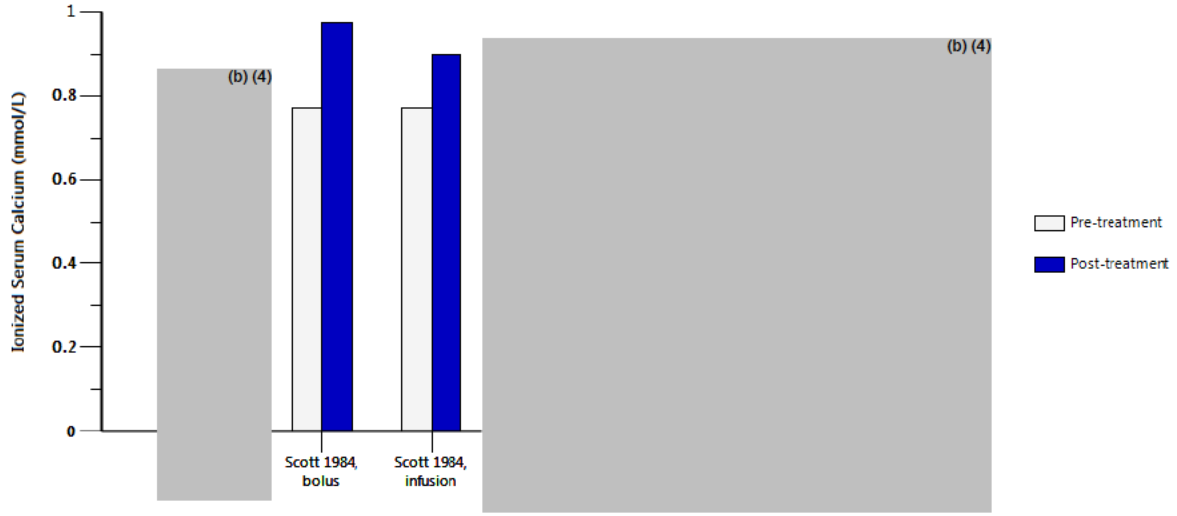
T= Calcium gluconate, P= Placebo control, R= Calcium chloride
*Both rows show different dose and/or route from the same publication [redacted] (b) (4)

Figure 1. Change in ionized serum calcium from baseline in the pivotal studies*.



*Note Buchta et al. reported only the percentage change in ionized calcium without reporting the baseline ionized serum calcium level and therefore this study was not included in this Figure. For detailed description of the studies listed on x-axis see Table 2.

Figure 2. Pre-treatment and post-treatment ionized serum calcium in the pivotal studies for neonates*.



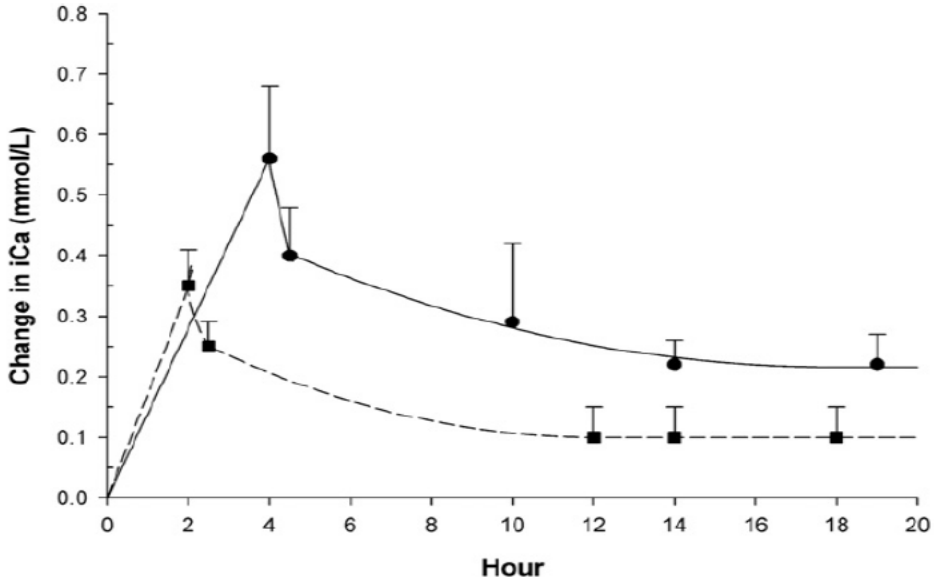
*For detailed description of the studies listed on x-axis see Table 2.

Figure 3. Pre-treatment and post-treatment ionized serum calcium in the pivotal and supportive studies for adults[a,b]

[a]Among the pivotal studies for adults (b) (4) and Buchta, 2003) only (b) (4) reported (b) (4)

Additionally, non-randomized supportive studies by (b) (4) (b) (4)

Figure 4. Dose-dependent pharmacokinetic characteristics of a short-term IV calcium gluconate* infusion in critically ill, adult trauma patients with hypocalcemia.



*The closed circles and solid line represent changes in ionized calcium (iCa) after a 4 h, 4 g IV calcium gluconate infusion. The closed squares and dashed line represent changes in iCa after a 2 h, 2 g IV calcium gluconate infusion.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing is reasonable from a clinical pharmacology perspective. See below for the literature evidence submitted by the sponsor for the different patient populations and corresponding reviewer's comment.

Adults

Dosing recommendations for adults were developed from 2 randomized clinical trials (RCTs) in adults involving 32 patients with hypocalcemia (Buchta, 2003; [redacted]) and 4 non-randomized clinical trials involving 621 patients with hypocalcemia ([redacted]).

The sponsor suggests an initial IV infusion dose of 1000 – 2000 mg/dose (10 – 20 mL) of calcium gluconate injection, [redacted] over [redacted] minutes for the correction of hypocalcemia-related symptoms in adult patients. The dose should be diluted in 5% glucose or normal saline (1:1 to 1:5). Careful monitoring for cardiac arrhythmias during infusion should be performed. The dose can be repeated every [redacted] depending on the responses of patients ([redacted]). Measurement of serum calcium every 4 to 6 hours is also suggested. In case of rapid IV bolus of calcium gluconate is required, monitoring of ECG during IV bolus administration is suggested and the rate of IV administration should not exceed 200 mg/minute (American Heart Association, 2005; Cooper, 2008). [redacted] for the correction of hypocalcemia related syndrome in adult patients is supported by published review articles ([redacted]) and [redacted].

Alternatively, after the first IV infusion dose of 1000 – 2000 mg, calcium gluconate can be continuously infused at a dose of [redacted] mg ([redacted] mg of elemental calcium), diluted in [redacted] 5% glucose, at an infusion rate of calcium gluconate 10% of 5.4 to 21.5 mg/kg/hour ([redacted]). The proposed dosing recommendations for adult patients with hypocalcemia are further supported by clinical data from pivotal and supportive studies in adult patients with hypocalcemia. Clinically, a single IV infusion dose of [redacted] of calcium gluconate 10% for adult patients with mild hypocalcemia and a total IV infusion dose of [redacted] for adult patients with severe hypocalcemia have been shown to be safe and effective ([redacted].

Reviewer's comment:

The IV calcium gluconate doses used in the pivotal randomized and the non-randomized studies ranged from 1 g to [redacted] A retrospective study by [redacted]. showed that [redacted]

(b) (4)

(b) (4)

The doses, dosing frequency and route for adult population are supported by (b) (4)

(b) (4)

(b) (4)

Pediatrics

Dosing recommendations for pediatric patient ages 1 month to less than 17 years were developed from 1 RCT involving 20 pediatric patients ages 1 day to 17 years with hypocalcemia (Broner, 1990) and at least 3 non-randomized clinical studies involving at least 5 patients with hypocalcemia ((b) (4); (b) (4); (b) (4)).

The initial dose of 29 mg/kg/dose calcium gluconate 10% is supported by a pivotal clinical study on hypocalcemic patients (Broner, 1990). The use of a dose of (b) (4) or a maximum single dose of (b) (4) is supported by case reports in pediatric patients ((b) (4); (b) (4); (b) (4); (b) (4)). Further support for the proposed dosing regimen of calcium gluconate 10% in pediatric patients 1 month to < 17 years of age was provided in a review article. One of the authors noted that a dose of (b) (4) of calcium gluconate 10% (b) (4) ((b) (4)). The proposed (b) (4) for pediatric patients ages 1 month to < 17 years is in agreement with (b) (4) and is in line with the recommendation (60 mg/kg/ (b) (4)) by the American Academy of Pediatrics to correct hypocalcemia in pediatric patients (The American Academy of Pediatrics, 1998). In addition, a single dose should not exceed (b) (4) as this dose range ((b) (4)) has been proven to be safe and effective in pediatric patients aged 1 month – < 17 years ((b) (4)). To maximize the cardiovascular safety of IV infusion of calcium gluconate 10% in pediatric patients, the sponsor proposes that FK USA's calcium gluconate injection, (b) (4) should be diluted with 5% dextrose or normal saline (ie, 1:1 to 1:5 dilution) and (b) (4), with careful monitoring for cardiac arrhythmias ((b) (4); (b) (4)). Measurement of serum calcium level every 4 – 6 hour is required. In case of rapid IV bolus of calcium gluconate is required, monitoring of ECG during IV bolus administration is suggested and the rate of IV administration should not exceed 100 mg/minute (Scott, 1984).

Reviewer's comments:

Broner et al. used 1 dose of 29 mg/kg/dose of calcium gluconate producing a significant increase in the mean serum ionized calcium level compared with the pretreatment level (Broner, 1990). The Advanced Pediatric Life Support (APLS) and guidance published by the American Academy of Pediatrics recommend a dose of 60 mg/kg in pediatrics. 4 case reports were used by the sponsor to support the dose in the pediatric patients with symptomatic and non-symptomatic hypocalcemia. Following are the brief summaries of these case reports:

– (b) (4)

- [redacted]
- [redacted]
- [redacted]

In summary, although the body of evidence is sparse, the proposed dose range of [redacted] mg/kg/dose is within the dosing used in the published literature and that recommended by APLS.

Neonates

Dosing recommendations for neonatal patients were developed from 3 RCTs in neonatal patients involving 76 neonates with hypocalcemia [redacted]; [redacted]; Scott, 1984) and 7 non-randomized clinical trials involving 78 neonatal patients with hypocalcemia (Brown, 1982; [redacted]; [redacted]; [redacted]; [redacted]; Salsburey, 1982; Venkataraman, 1985a; Venkataraman, 1985b).

The sponsor proposes that an IV infusion dose of 100 – 200 mg/kg (1 – 2 mL/kg) of calcium gluconate injection, [redacted] repeated every 6 hours if needed for the treatment of hypocalcemia-related symptoms in neonatal patients (ages < 1 month). This dose range and infusion rate have been shown to effectively increase plasma calcium levels and relieve the hypocalcemia-related symptoms in neonatal population as seen in the pivotal randomized placebo controlled studies in neonates with hypocalcemia [redacted]; [redacted]; Scott, 1984). The MDD of IV calcium gluconate for neonatal patients is 800 mg/kg/day, divided in at least 4 separated doses for every 6 hour (Scott, 1984; Taketomo, 2014). Alternatively, after the first dose, calcium gluconate can be continuously IV infused at a dose of [redacted] ([redacted]; [redacted]). To maximize the cardiovascular safety of IV infusion of calcium gluconate 10% in neonates, the sponsor proposes that calcium gluconate injection, [redacted] should be diluted with 5% dextrose or normal saline (ie, 1:1 to 1:5 dilution) and infused [redacted] with careful monitoring for cardiac arrhythmias ([redacted]).

Reviewer's comments:

The dose of 100 – 200 mg/kg and the dosing frequency of every 6 hours are supported by Scott et al., [redacted]. and [redacted]. ([redacted] Scott, 1984; [redacted]). [redacted]

(b) (4) infused the dose (b) (4) Scott et al. administered 200 mg/kg dose every 6 hours thus covering the 800 mg/kg MDD.

In summary, the dosing recommendations in the neonate population are well covered by the published literature.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No, there is no need for dosage adjustment for renal and hepatic impaired subpopulation and in the geriatric patients. See below for the literature evidence submitted by the sponsor and reviewer's comment.

Patients with Hepatic Impairment

It is known that the ionized calcium value may be normal when the total calcium value is high or low, depending on serum albumin concentrations (Zhou, 2009). The effects of hepatic function on calcium gluconate have been investigated in the anhepatic stage of liver transplantation; data have shown that the availability of ionized calcium after calcium gluconate IV administration was not affected by the absence of hepatic function (Bull, 1980; Cote', 1987; Heining, 1984; (b) (4) It was noted that, in patients with preascitic cirrhosis patients, a dose of 2 g calcium gluconate (~ 20 mL of FK USA's calcium gluconate injection, USP 10%) infusion over 60 minutes was well tolerated and no unexpected AEs were noted (Sansoe, 2007). Therefore, dosing adjustment of calcium gluconate in hepatic impaired patients may not be necessary. However, the total dose is dependent upon the serum calcium levels of patients.

Reviewer's comment:

In a study by Sansoe et al. 10 patients with preascitic cirrhosis and 9 age-matched control volunteers (with no history of liver, renal or cardiac diseases) were given 60 min infusion of 33 mg/min calcium gluconate diluted in 100 ml of 5% glucose solution (Sansoe, 2007). IV infusion of calcium significantly increased the serum calcium concentrations in both patients with cirrhosis and in controls (respectively, from 2.0 (0.1) to 2.4 (0.2) mmol/L, and from 2.1 (0.4) to 2.5 (0.1) mmol/L) and 3 h urinary calcium excretion rate by 0.26 and 0.15 mmol/h in control and cirrhosis group respectively. Bull, 1980; Cote', 1987 and Henning 1984 studies do not the support sponsor's claim as the study was not aimed to study calcium gluconate in hepatic impairment.

(b) (4)

(b) (4)

The data support the efficacy of calcium gluconate for increasing serum ionized calcium concentration above the threshold of symptomatic hypocalcemia.

In summary, both Sansoe et al. and (b) (4) show that approximately 2 g of dose was efficacious in hepatic impaired population. Thus, no dose adjustment is needed in hepatic impaired patients.

Patients with Renal Impairment

Renal elimination is not the major clearance mechanism of calcium. However, patients with renal dysfunction have an increased risk of hypercalcemia. Periodically checking the serum calcium level is recommended when IV calcium gluconate is administrated. (b) (4)

(b) (4)

(b) (4)

Monitoring serum calcium level every 4 hour is also recommended (Loke, 2009). Therefore, the lower limit of the dose ranges for age groups of calcium gluconate injection, (b) (4) should be initiated. The infusion time (b) (4) serum calcium levels of patients.

Reviewer's comment:

The labeling language proposed by the sponsor – ' (b) (4) ' is not applicable to all renal impaired patients. In the publication (b) (4) state – (b) (4)

(b) (4)

In summary, there is scarcity of data to inform dosing in the renal impaired patients. A lower dose between [redacted] was used by [redacted]. in the study. Renal impairment may be associated with hypercalcaemia and secondary hyperparathyroidism. Therefore, to patients with renal impairment, parenteral calcium should be administered only after careful assessment of the indication and the calcium-phosphate balance should be monitored.

Geriatric Patients

No differences in efficacy between elderly and younger patients were identified in studies conducted in both geriatric and younger patients with regard to the increase of serum calcium levels ([redacted]; Suzuki, 1988) or with regard to correction of hypocalcemia-related symptoms (Belluzzo, 2011). No efficacy differences associated with the administration of IV administration of calcium gluconate for the correction of hypocalcemia in the geriatric patients were reported in the published studies (Belluzzo, 2011; [redacted] Suzuki, 1988)

Intravenous calcium gluconate has been administrated in geriatric patients for conditions associated with and without hypocalcemia. No clinical experience has identified differences in response between the elderly and younger patients or specific safety issues associated with administration in geriatric populations. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Reviewer's comment:

[redacted] In Belluzzo et al. study a 74-year-old woman experiencing a generalized tonic-clonic seizure was given IV calcium gluconate supplementation and the total calcium serum level increased from 1.2 mmol/L (normal range 2.1– 2.8 mmol/L) to 1.9 mmol/L. However, the dose of calcium gluconate was not specified. In Suzuki et al. study subjects aged 43-83 years received calcium infusion (8.5% calcium gluconate solution at a rate of 7.5 mg/kg per h for 1 h) increasing the concentration of serum calcium from 2.2 ± 0.1 to 3.2 ± 0.2 mmol/L and from 2.2 ± 0.1 to 3.2 ± 0.1 mmol/L in normotensives (n = 20) and hypertensives (n = 12), respectively (Suzuki, 1988).

In summary, limited data available in the geriatric population shows that [redacted]. The efficacy of calcium gluconate in geriatric population appears similar to adult.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The following DDIs were proposed by the sponsor:

Cardiac glycosides: it has been noted that IV calcium should be administered very cautiously to a patient who is digitalized or who is taking effective doses of digitalis or digitalis-like preparations. The synergistic arrhythmias may occur if calcium and digitalis are given together (Levine, 2011; Morgan, 1985; Roxane Laboratories, 2012). Although the inotropic and toxic effects of cardiac glycosides and calcium is known, a review of medical data found no life-threatening arrhythmias occurred within 1 h of calcium administration in patients with digoxin toxicity. However, if considered necessary, calcium should be given slowly in small amounts and close ECG monitoring is recommended (Ahee, 2000; Erickson, 2008).

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Ceftriaxone: concurrent use of IV ceftriaxone and calcium-containing solutions may cause life-threatening adverse drug reaction (Bradley, 2009; Dalton, 2010). Concomitant use of ceftriaxone and IV calcium-containing products is contraindicated in neonates (≤ 28 days of age) due to the formation of ceftriaxone-calcium precipitates. Ceftriaxone should not be used in neonates if they are receiving or are expected to receive calcium-containing IV products. In patients > 28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid. Ceftriaxone must not be administered simultaneously with IV calcium-containing solutions via a Y-site in any age group (Ceftriaxone label, 2009).

Vitamin D: Vitamin D increases the gastrointestinal absorption of calcium (eg, from dietary sources) (Christakos, 2011). High vitamin D intake should be avoided during calcium therapy unless especially indicated. Plasma calcium concentrations should be monitored in patients taking these drugs concurrently.

Calcium channel blockers: Administration of calcium may reduce the response to verapamil and possibly other calcium channel blockers (Ashraf, 1995; Woie, 1981).

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Diuretics: Concurrent use of thiazide diuretics with calcium may result in hypercalcemia, as thiazide diuretics reduce urinary calcium excretion. Serum calcium levels should be monitored in patients receiving these drugs concurrently (Salix Pharms, 2009). Prolonged concurrent use of furosemide diuretics with calcium may result in hypercalciuria and increase urinary calcium excretion may lead to urinary lithiasis (Goldsmith, 1981).

Phosphate and bicarbonate: calcium should not be mixed with fluids containing phosphate or bicarbonate to avoid precipitation (Cooper, 2008; Zhou, 2009).

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Reviewer's comments:

After reviewing the prescribing information of the drugs for DDI with calcium gluconate, the proposed language for interactions with cardiac glycosides, ceftriaxone, calcium channel blockers and phosphate/bicarbonate containing solutions were considered acceptable. (b) (4)

[redacted]

However, another antibiotic of the same class - minocycline has been reported to be incompatible with IV calcium gluconate (Refer to minocycline prescribing information). DDI language for relevant tetracycline antibiotics showing interaction with IV calcium administration will be reflected in the label. The proposed interactions with Vitamin D, calcitonin, thiazide diuretics and impact of IV calcium administration will be reflected in the Warnings and Precautions section rather than the DDI section. Similarly, drugs mentioned below can affect the calcium levels directly/indirectly and could be reflected in the Warnings and Precautions section (section 5):

- Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

- Rifampin has been reported to alter vitamin D metabolism. In some cases, reduced levels of circulating 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D have been accompanied by reduced serum calcium and phosphate, and elevated parathyroid hormone.

- There is evidence that calcipotriene can be absorbed in amounts that are sufficient to produce systemic effects, including elevated serum calcium; hypercalcemia has been observed in normal prescription use. Use calcipotriene cautiously with other agents that can produce hypercalcemia

- Teriparatide transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Severe hypercalcemia has been reported with parathyroid hormone

Other drug interactions (eg. ciprofloxacin, phenytoin, neuromuscular blockers, levothyroxine, iron preparations, multivitamins and alendronate) were reviewed, however, were deemed not applicable to this IV product since they were absorption related.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The summary of bioanalytical method used for the pivotal studies is listed in Table 3. In most cases an ionized calcium analyzer (ICA) was used. The instrument measures pH and calcium ion concentration and makes an adjustment of the latter with respect to the actual pH (to pH 7.4) according to a built-in algorithm in the interval pH 7.2-7.6. This simultaneous measurement of the ionized calcium and pH is advantageous as it eliminates the routine problem of pH dependent binding of calcium to albumin. Serum is pumped through the electrode to make contact with a porous membrane impregnated with a liquid ion-exchanger. This ion-exchanger selectively binds calcium and is normally saturated with that ion. A potential difference is set up between the ionized calcium of the serum and that of the liquid ion-exchanger. Since the calcium concentration of the saturated ion-exchanger is constant, the potential difference established is dependent only on the ionized calcium concentration of the serum. This technique is generally considered to have good precision (within batch CV% of 0.6% and between batch CV% of 2.11%) with linear over a linear range of 0.35 to 2.90 mmol/L and with little interference from other cations (Smith, 1983).

Table 3. Summary of bioanalytical assay used in the six pivotal studies.

Pivotal studies	Bioanalytical
(b) (4)	
Scott, 1984	Ionized calcium concentrations (Orion SS·20 ionized calcium analyzer) and pH (Radiometcr E5021) were measured within 20 min of sampling using whole blood obtained from an umbilical artery catheter in a syringe into which l ml heparin had been drawn and then totally expelled.
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Broner, 1990	Blood for ionized calcium levels was obtained, placed in heparinized containers (Radiometer A/S, Copenhagen, Denmark) on ice water, and evaluated immediately. All samples were analyzed on the Radiometer ICA IE Ionized Calcium Analyzer within 5 min of time of collection.
Buchta, 2003	Serum levels of ionized calcium were determined by an automatic electrolyte analyzer (AVL 984-S, Schaffhausen, Switzerland).
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4.2 Summary of the six pivotal studies

Study Synopsis: (b) (4)

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Study Synopsis: Effect of calcium therapy in the sick premature infant with early neonatal hypocalcemia

Study Title: Effect of calcium therapy in the sick premature infant with early neonatal hypocalcemia (**Scott, 1984)**	
Location	USA (St. Louis Children Children's Hospital)
Study Design	Randomized controlled
Population Demographics	• 18 neonates with early neonatal hypocalcemia • Subjects were randomized to 1 of 3 groups (n = 9/group): placebo, calcium gluconate IV bolus or calcium gluconate IV drip. However, if ionized calcium < 2.5 mg/mL the subjects were randomized to either IV bolus or IV drip group: • Exclusion criteria: not reported
Hypocalcemia	Hypocalcemia definition: Total serum calcium < 6.0 mg/dL (1.5 mmol/L). Symptomatic hypocalcemia: 1 patient had ionized calcium < 2.5 mg/mL. The patient was symptomatic (jitteriness)
Treatment (per arm)	• IV bolus treatment arm: IV bolus dose of 200 mg/kg/dose (2 mL/kg of calcium gluconate 10%) at a rate of 100 mg/minutes every 6 hours. If the ionized calcium > 3.5 mg/dL, the subjects were removed from treatment and observed every 6 hours until a total of 24 hours of treatment or sampling has been completed. • IV infusion arm (drip): continuous IV infusion of 400 mg/kg/day. If the ionized calcium > 3.5 mg/dL, the subjects were removed from treatment and observed every 6 hours until a total of 24 hours of treatment or sampling has been completed. • Controlled arm: no calcium was provided
Assessment	Serum total, ionized calcium and hypocalcemic sign were assessed before the treatment and every 6 hours following the administration of calcium gluconate or placebo.
Endpoints and related definitions	Endpoints were the changes in total and ionized serum calcium, correction of symptom-related hypocalcemia (irritability, jitteriness, and twitching)

Study Title: Effect of calcium therapy in the sick premature infant with early neonatal hypocalcemia (**Scott, 1984)**	
Efficacy results related to calcium gluconate	• Mean ionized calcium from the bolus and drip groups were significantly increased at times 6 and 24 hours, compared to time zero. However, mean ionized calcium from the bolus group was greater than that of drip at time 24 hours. • Mean ionized calcium from the control group was only significantly increased at time 24 hours compared to time zero. • By 24 hours, in all groups, total calcium had increased to greater than 6.0 mg/dL (bolus 6.5 ± 1.1, drip 7.0 ± 0.4, control 6.6 ± 0.4) and ionized calcium to greater than 3.5 mg/dL (bolus 3.9 ± 0.3, drip 3.6 ± 0.6, control 3.6 ± 0.3). • There was 1 hypocalcemic subject with symptoms, and the symptoms as well as low ionized calcium level (< 2.5 mg/dL) of this subject were successfully treated with an IV bolus dose of calcium gluconate.
Safety Data	ECG findings were not related to total and ionized calcium levels. Lack of relation between QT segment, serum albumin and pH to ionized calcium

Study Synopsis: (b) (4)

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Study Synopsis: Reduction of adverse citrate reactions during autologous large-volume PBPC apheresis by continuous infusion of calcium-gluconate

Study Title: Reduction of adverse citrate reactions during autologous large-volume PBPC apheresis by continuous infusion of calcium-gluconate (**Buchta, 2003**)	
Location	Austria (University Hospital of Vienna)
Study Design	Randomized, double blinded, placebo controlled
Population Demographics	• 25 adults with malignant diseases and autologous large volume peripheral blood progenitor cells apheresis • Subjects were randomized to treatment (n=25) or placebo (n = 25) groups • Exclusion criteria: Patients with signs of an abnormal electrocardiographic conductivity were excluded from the study. Only patients during their first apheresis course were included
Hypocalcemia	Hypocalcemia was expected during autologous large volume peripheral blood progenitor cells apheresis due to citrate
Treatment (per arm)	• Treatment arm: infusion of ~ 4000 mg of calcium gluconate diluted in 500 mL of saline at a rate of 100 mL/hour (~760 mg calcium gluconate/hour) • Placebo arm: infusion of 500 mL saline
Assessment	Serum total calcium, potassium, phosphorus were assessed before and after the treatment
Endpoints and related definitions	Assessment of the effectiveness of continuous IV administration of calcium gluconate during autologous large volume peripheral blood progenitor cells (PBPC) collection
Efficacy results related to calcium gluconate	• Continuous calcium support throughout PBPC apheresis led to a less pronounced decrease in serum calcium (-10.4 ± 6.5%) compared to the placebo-treated group (-26.9 ± 10.4%; $p<0.0001$). • Total calcium levels increased in the treatment group by 6.9 ± 5.4 % compared to a decrease of 4.2 ± 5.9 % in the control group receiving saline ($p < 0.0001$). • Continuous administration of calcium gluconate reduced the incidence of symptomatic hypokalemia by 65 % (4/24 patients in calcium groups vs 12/25 patients in control group)
Safety Data	The administration of calcium was not associated with technical problems related to the apheresis procedure and number of CD34+ cells

Study Synopsis: A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children

Study Title: A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children (**Broner, 1990**)	
Location	USA (Le Bonheur Children's Medical Center)
Study Design	Randomized, active controlled
Population Demographics	• 20 critically ill children (aged 1 day – 17 years) in the intensive care unit. • Subjects were randomized to 2 groups: calcium gluconate (n = 20) or calcium chloride (n=17): • Exclusion criteria: not reported
Hypocalcemia	Hypocalcemia: Ionized calcium: 1.03 ± 0.14 vs 1.07 ± 0.12 mmol/L for calcium chloride vs calcium gluconate group, respectively
Treatment (per arm)	• Calcium gluconate arm: a single dose of elemental calcium 0.136 mEq/kg (~ 29 mg/kg calcium gluconate 10%) • Calcium chloride arm: a single dose of elemental calcium 0.136 mEq/kg
Assessment	Serum ionized calcium levels were assessed before and 30 minutes after the treatment Arterial pH levels, renal and hepatic functions, and serum electrolytes were obtained on admission or within 12 hours after initial ionized calcium measurements
Endpoints and related definitions	Endpoints were the changes in ionized serum calcium and severity of illness.
Efficacy results related to calcium gluconate	• A single dose of 29 mg/kg/dose of calcium gluconate 10% produced a significant increase in the mean serum ionized calcium level compared with the pretreatment level ($p < 0.05$). • The mean increase in ionized calcium levels was 0.19 mmol/L for the chloride group and 0.09 mmol/L for the gluconate group ($p < 0.05$).
Safety Data	There was no significant change in the mean pH or in heart rate after treatment with either salt. An increase in mean arterial pressure of nearly 6 mm Hg was observed in calcium chloride treated group ($p < 0.05$). No change in blood pressure was seen in the group receiving calcium gluconate.

Study Synopsis (b) (4)

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