APPLICATION NUMBER:

208418Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
## Office of Clinical Pharmacology Review

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<td>Submission Date</td>
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<td>Submission Type</td>
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<td>Brand Name</td>
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<td>Generic Name</td>
<td>Calcium gluconate injection, USP 10%</td>
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<tr>
<td>Dosage Form and Strength</td>
<td>Injection, 10%</td>
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<tr>
<td>Route of Administration</td>
<td>Intravenous</td>
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<tr>
<td>Proposed Indication</td>
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<td>Applicant</td>
<td>Fresenius Kabi USA, LLC</td>
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<td>Associated IND</td>
<td>IND 113171</td>
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<tr>
<td>OCP Review Team</td>
<td>Renu Singh, PhD</td>
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<td>OCP Final Signatory</td>
<td>Jayabharathi Vaidyanathan, PhD (Team Leader)</td>
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1. EXECUTIVE SUMMARY

Fresenius Kabi USA seeks approval of calcium gluconate injection, USP 10% for the (b)(4) via the regulatory 505(b)(2) pathway. The applicant’s calcium gluconate injection 10%, USP 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 textbooks 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:

<table>
<thead>
<tr>
<th>Review Issue</th>
<th>Recommendations and Comments</th>
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<tr>
<td>Pivotal or supportive evidence of effectiveness</td>
<td>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.</td>
</tr>
<tr>
<td>General dosing instructions</td>
<td>The proposed dosing is acceptable.</td>
</tr>
<tr>
<td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td>
<td>The proposed dosing is acceptable.</td>
</tr>
<tr>
<td>Labeling</td>
<td>See section 2.4 for labeling.</td>
</tr>
<tr>
<td>Other (specify)</td>
<td>None</td>
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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% to 10% serum calcium is bound to organic and inorganic acids (e.g., 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 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
  - Ceftriaxone
  - Vitamin D
  - Calcium channel blockers
  - Diuretics
  - Phosphate and bicarbonate

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 phosphate and bicarbonate contained within the DDI section was suggested. 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, USP 10%.

The sponsor submitted an initial pediatric study plan (iPSP) on July 27, 2015. The Agency requested additional justification for the maximum daily dose (MDD) for neonates. The Agency did not agree with the sponsor’s original intentions and instead asked for additional literature data to support the safety and efficacy as well as the MDD 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 MDD for neonates was provided. However, per FDA feedback, 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 600 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 Brown et al. evaluated two different doses – a high dose of 600 mg/kg/day followed by 300 mg/kg/day and a low dose of 200 mg/kg/day followed by 100 mg/kg/day (Brown, 1981). The authors reported a higher ionized calcium level with the higher dose as compared to the lower dose. For adult population Dickerson et al. (2007a) used a dose of 2 g and 4 g for mild (ionized calcium 1 – 1.12 mmol/L) and severe (ionized calcium < 1 mmol/L) hypocalcemic patients, respectively. Figure 4 shows a dose-dependent PK in this non-randomized single-arm study. Thus, there is limited evidence of dose-response or dose-proportionality. It should be noted that the ionized calcium was measured at different timings in these studies. While Scott et al. and Brown et al. measured the ionized calcium at 24 hour, Porcelli et al. measurement was done at 3-6 hour. For adult studies the ionized calcium was measured at 30 min and 10 min by Broner et al. and Martin et al., 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.

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Dose</th>
<th>Frequency/Route</th>
<th>Formulation</th>
</tr>
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<tbody>
<tr>
<td>Porcelli 1995</td>
<td>Neonates (T=22, P=21)</td>
<td>100 mg/kg</td>
<td>Bolus, single dose</td>
<td>Ca gluconate (100 mg/mL)</td>
</tr>
<tr>
<td>Scott 1984*, bolus</td>
<td>Neonates (T=9, P=9)</td>
<td>200 mg/kg at 100 mg/min</td>
<td>Bolus, q6h</td>
<td>Ca gluconate</td>
</tr>
<tr>
<td>Scott 1984*, infusion</td>
<td>Neonates (T=9, P=9)</td>
<td>400 mg/kg/day</td>
<td>Continuous Infusion</td>
<td>Ca gluconate</td>
</tr>
<tr>
<td>Brown 1981*, high dose</td>
<td>Neonates (T=18, P=11)</td>
<td>600 mg/kg/day then 300 mg/kg/day</td>
<td>Bolus, q6h or Continuous infusion</td>
<td>Ca gluconate, 9% elemental</td>
</tr>
<tr>
<td>Brown 1981*, low dose</td>
<td>Neonates (T=18, P=11)</td>
<td>200 mg/kg/day then 100 mg/kg/day</td>
<td>Bolus, q6h or Continuous infusion</td>
<td>Ca gluconate, 9% elemental</td>
</tr>
<tr>
<td>Brown 1981*, bolus</td>
<td>Neonates (T=17, P=11)</td>
<td>200-600 mg/kg/day then 100-300 mg/kg/day</td>
<td>Bolus, q6h</td>
<td>Ca gluconate, 9% elemental</td>
</tr>
<tr>
<td>Brown 1981*, infusion</td>
<td>Neonates (T=19, P=11)</td>
<td>200-600 mg/kg/day then 100-300 mg/kg/day</td>
<td>Continuous infusion</td>
<td>Ca gluconate, 9% elemental</td>
</tr>
<tr>
<td>Buchta 2003</td>
<td>Adults (T=25, P=25)</td>
<td>3844 mg at 769 mg/hour</td>
<td>Bolus, single dose</td>
<td>Ca gluconate (Fresenius Kabi)</td>
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**Randomized positive-controlled studies**

<table>
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<tr>
<th>Source</th>
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<th>Dose</th>
<th>Frequency/Route</th>
<th>Formulation</th>
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<tr>
<td>Broner, 1990</td>
<td>1 day-17yr (T=20, R=17)</td>
<td>29 mg/kg/dose</td>
<td>Bolus, single dose</td>
<td>Ca gluconate</td>
</tr>
<tr>
<td>Martin, 1990</td>
<td>Adults (T=7, R=8)</td>
<td>30 mg/kg</td>
<td>Bolus, single dose</td>
<td>Ca gluconate</td>
</tr>
</tbody>
</table>

*T= Calcium gluconate, P= Placebo control, R= Calcium chloride
*Both rows show different dose and/or route from the same publication.
#All four rows show different dose and/or route from the same publication.
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\textsuperscript{a,b}

\textsuperscript{a}Among the pivotal studies for adults (Martin, 1990 and Buchta, 2003) only Martin et al. reported the baseline ionized calcium level whereas Buchta et al. reported only the percentage change in ionized calcium. Hence, for Figure 3 only Martin et al. study was used. Additionally, non-randomized supportive studies by Dickerson et al. (Dickerson, 2005; Dickerson 2007a; Dickerson 2007b) were plotted to show efficacy in the adults.

\textsuperscript{b}Dickerson 2005 severe and Dickerson 2005 mild represents two treatment groups from the same publication. Similarly Dickerson 2007a mild and Dickerson 2007a severe are two different treatment arms from the same publication. Dickerson 2007a and Dickerson 2007b are two separate publications from the same first author.

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

\textsuperscript{*}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; Martin, 1990) and 4 non-randomized clinical trials involving 621 patients with hypocalcemia (Dickerson, 2005; Dickerson, 2007a; Dickerson, 2007b; Steele, 2013).

The sponsor suggests an initial IV infusion dose of 1000 – 2000 mg/dose of calcium gluconate injection, USP 10% in adult patients. The dose should be diluted in 5% or normal saline. Careful monitoring for cardiac arrhythmias should be performed. The dose can be repeated every 4 – 6 hour depending on the responses of patients (American Heart Association, 2005; Cooper, 2008; French, 2012; Phebra Pty, 2013; Society for Endocrinology, 2013; Taketomo, 2014). Measurement of serum calcium 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). The sponsor’s proposed MDD of

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 1000 mg/hour of calcium gluconate 10% for adult patients with mild hypocalcemia and a total IV infusion dose of 4000 mg calcium gluconate over a period of 4 hours (total single dose 4000 mg calcium gluconate/4 hour) for adult patients with severe hypocalcemia have been shown to be safe and effective (Dickerson, 2005; Dickerson, 2007a; Dickerson, 2007b).

Reviewer’s comment:

The IV calcium gluconate doses used in the pivotal randomized and the non-randomized studies ranged from 1 g to 4 g. A retrospective study by Steele et al. showed that when 1 g dose of
Calcium gluconate was diluted in 20 mL of saline and infused in 30 min and was repeated daily for 4 days, ionized calcium levels normalized within 4 days in most patients (Steele, 2013). Dickerson et al. study used 1-4 g dose of calcium gluconate and showed that the relationship between dose and change in ionized calcium level (Figure 5) is not steep (Dickerson, 2005). Hence, the advantage of a higher dose might be limited to severe hypocalcemia cases. Caution needs to be exercised while using a high 4 g dose as hypercalcemia was reported in 10% of the patients (Dickerson 2007b). The doses, dosing frequency and route for adult population are supported by the guidelines from American Heart Association, 2005 (http://circ.ahajournals.org/content/112/24_suppl/IV-121) which states the following:

‘Treatment of hypocalcemia requires administration of calcium. Treat acute, symptomatic hypocalcemia with 10% calcium gluconate, 93 to 186 mg of elemental calcium (10 to 20 mL) IV over 10 minutes. Follow this with an IV infusion of 540 to 720 mg of elemental calcium (58 to 77 mL of 10% calcium gluconate) in 500 to 1000 mL 5% dextrose in water at 0.5 to 2 mg/kg per hour (10 to 15 mg/kg). Alternatively, administer 10% calcium chloride, giving 5 mL (136.5 mg of elemental calcium) over 10 minutes, followed by 36.6 mL (1 g) over the next 6 to 12 hours IV. Measure serum calcium every 4 to 6 hours. Aim to maintain the total serum calcium concentration at 7 to 9 mg/dL. Correct abnormalities in magnesium, potassium, and pH simultaneously. Note that untreated hypomagnesemia will often make hypocalcemia refractory to therapy. Therefore, evaluate serum magnesium when hypocalcemia is present and particularly if hypocalcemia is refractory to initial calcium therapy.’

Figure 5. Correlation between calcium gluconate dose normalized to body weight (mg/kg) and change in serum ionized calcium (iCa) concentration.
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 (Helikson, 1997; Raffaella, 2009; Thakur, 2008).

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 60 mg/kg/dose or a maximum single dose of 80 mg/kg/dose is supported by case reports in pediatric patients (Devlin, 1990; Helikson, 1997; Raffaella, 2009; Thakur, 2008). 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 50 mg/kg of calcium gluconate 10% is sufficient to eliminate hypocalcemia-related symptoms in pediatric patients and has not been associated with arrhythmias (Zhou, 2009). The proposed MDD for pediatric patients ages 1 month to < 17 years is in agreement with elemental calcium dosing recommendation from an approved calcium product for the correction of hypocalcemia in pediatric patients (Approved Calcium Chloride Hospira Label NDA 021117, revised 2009) and is in line with the recommendation (60 mg/kg/dose, repeat as needed for desired clinical effect) by the American Academy of Pediatrics to correct hypocalcemia in pediatric patients (The American Academy of Pediatrics, 1998).

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, USP 10% should be diluted with 5% dextrose or normal saline and infused slowly with careful monitoring for cardiac arrhythmias (Cooper, 2008; Jain, 2010; Zhou, 2009). 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:

- Raffaella, 2009- A 5-year-old male patient was given IV calcium gluconate 200 – 300 mg/kg/day for 9 days and reduced to 50 – 100 mg/kg/day for 6 days until normalization of calcium serum levels. This publication does not specify the frequency at which the dose was administered. With the proposed dose of 29 mg/kg/dose by the sponsor and a frequency of 4 times a day, the range of daily dose for pediatric patients is mg/kg/day or mg/kg/day.
- Thakur, 2008 - 3 children (4, 10 and 15 years old; 1 M/2 F) were given 20 ml of 10 percent (89 mg of elemental calcium/10 ml) gluconate. The body weights of children were not reported in this publication; hence an accurate assessment of mg/kg dose was not possible in this case.

- Helikson, 1997 - A 3-year-old female patient (18 kg) was given IV infusion, 1 g/dose × 2 doses of calcium gluconate. In this case the patient was given 55 mg/kg dose of calcium gluconate and supports the dosing proposed by the sponsor.

- Devlin, 1990 - 2 pediatric patients (1 M/1 F; a 4 year old and an 8.5-year old) were given IV infusion of calcium gluconate 10% at a dose of 2900 mg/day (6.75 mmol calcium/24 hour which equals to ~ 3 doses of 1000 mg/dose) was given to the 4 year-old child. IV infusion of 1000 mg calcium gluconate 10% over 5 hours was given to 8.5-year old child. The body weights of children were not reported in this publication; hence an accurate assessment of mg/kg dose was not possible in this case.

In summary, although the body of evidence is sparse, the proposed dose range of 29 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 (Brown, 1981; Porcelli, Jr., 1995; Scott, 1984) and 7 non-randomized clinical trials involving 78 neonatal patients with hypocalcemia (Brown, 1982; Fishbein, 1982; Kurt, 2006; Mirro, 1984; Roberts, 1977; Salsbury, 1982; Venkataraman, 1985a; Venkataraman, 1985b).

The sponsor proposes that an IV infusion dose of 100 – 200 mg/kg of calcium gluconate injection, USP 10%, 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 (Brown, 1981; Porcelli, Jr., 1995; 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).

To maximize the cardiovascular safety of IV infusion of calcium gluconate 10% in neonates, the sponsor proposes that calcium gluconate injection, USP 10% should be diluted with 5% dextrose or normal saline and infused with careful monitoring for cardiac arrhythmias (Doyle, 2011).

Reviewer’s comments:

The dose of 100 – 200 mg/kg and the dosing frequency of every 6 hours are supported by Scott et al., Porcelli et al. and Brown et al. (Porcelli, Jr., 1995; Scott, 1984; Brown, 1981). Porcelli et
al. infused the dose over 30-60 min (Porcelli, Jr., 1995). 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; Martin, 1990). 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.

Martin et al. published a randomized, comparative controlled study in 15 adult patients with liver transplantation (mean age 40 ± 11.8 years) (Martin, 1990). During the anhepatic stage, a single IV dose of ~ 30 mg/kg calcium gluconate (~ 1800 mg calcium gluconate for an adult of 60 kg) was administrated to hypocalcemic patients (n = 7 for calcium gluconate and n = 8 for calcium chloride). The results showed that equal ionized calcium concentration increased rapidly after the administration of either of the salt forms. In the calcium gluconate treated group, ionized serum calcium increased form 0.74 ± 0.11 to 1.05 ± 0.10 and 0.93 ± 0.10 and 0.89 ± 0.09 after 1, 5 and
10 min after the administration. The subjects with symptomatic hypocalcemia were not described. However, it is clear that some subjects had predose serum ionized calcium levels ≤ 0.7 mmol/L [the threshold of symptomatic hypocalcemia (French, 2012; Sorell, 1975)]. After 1–10 min of calcium gluconate administration, the authors showed that all the subjects had serum ionized calcium above the threshold of symptomatic hypocalcemia. 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 Martin et al. 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. Slow infusion of calcium gluconate over 20 to 30 min is recommended for adult patients with acute renal failure (Ahee, 2000). In patients with moderate to severe chronic renal failure and secondary hyperparathyroidism, calcium gluconate infusion did not affect the left ventricle dimensions or fractional shortening but impaired diastolic function (Virtanen, 1998). In a retrospective study, to prevent postoperative hypocalcemia in chronic stage 4 to stage 5 renal failure adult patients, who underwent parathyroidectomy because of secondary hyperparathyroidism. The titration of calcium gluconate 10% at 450 mg/hour when serum calcium < 2 mmol/L, increased to 650 mg/hour and to 900 mg/hour if serum calcium continued falling has been shown to be effective, and no significant AEs were recorded (Loke, 2009). The authors concluded that titration regimen should be made depending upon the calcium serum levels in patients with renal impairment. 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, USP 10% should be initiated. The infusion time should be prolonged to a rate of 900 mg/hour in adult subjects with chronic renal impairment. The total dose is dependent on the serum calcium levels of patients.

Reviewer’s comment:
The labeling language proposed by the sponsor –

(b)(4)
In summary, there is scarcity of data to inform dosing in the renal impaired patients. A lower dose between 450 mg to 900 mg was used by Loke et al. 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 (Grau, 1996; 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; Grau, 1996; 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:**

In Grau et al. study 11 cancer patients and 11 control subjects received calcium gluconate, 4 mg/kg IV infusion during cisplatin therapy (Grau, 1996). The ionized calcium before and after therapy were 1.22 ± 0.52 and 1.11 ± 0.07 mmol/L respectively in control group and 1.20 ± 0.1 and 1.28 ± 0.08 mmol/L respectively in the treatment group. However, the age of subjects ranged from 16-73 years and the publication does not specify the number of elderly subjects. 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 a lower dose of 240 to 450 mg dose (based on 60 kg body weight) was used in this population. 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).

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).

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 Pharmas, 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).
Calcium gluconate injection has been reported to be incompatible with IV solutions containing various drugs. Published data are too varied and/or limited to permit generalizations, and specialized reference should be consulted for specific information.

**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.

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.

<table>
<thead>
<tr>
<th>Pivotal studies</th>
<th>Bioanalytical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcelli, 1995</td>
<td>Total serum calcium was measured by colorimetric analysis on a Dade (Baxter) Paramax analyzer (Miami, FL). Ionized serum calcium was measured using Radiometer ICA-I analyzer (Westlake, OH).</td>
</tr>
<tr>
<td>Scott, 1984</td>
<td>Ionized calcium concentrations (Orion SS·20 ionized calcium analyzer) and pH (Radiometer E5021) were measured within 20 min of sampling using whole blood obtained from an umbilical artery catheter in a syringe into which 1 ml heparin had been drawn and then totally expelled.</td>
</tr>
<tr>
<td>Brown, 1981</td>
<td>Institutional hospital-based technique was employed. No details were provided.</td>
</tr>
<tr>
<td>Broner, 1990</td>
<td>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.</td>
</tr>
<tr>
<td>Buchta, 2003</td>
<td>Serum levels of ionized calcium were determined by an automatic electrolyte analyzer (AVL 984-S, Schaffhausen, Switzerland).</td>
</tr>
<tr>
<td>Martin, 1990</td>
<td>Ionized calcium concentration was determined by use of an ICA-1 Ionized Calcium Analyzing System (Radiometer, Copenhagen)</td>
</tr>
</tbody>
</table>
### 4.2 Summary of the six pivotal studies

**Study Synopsis: Effects of single dose calcium gluconate infusion in hypocalcemic preterm infants**

<table>
<thead>
<tr>
<th>Study Title: Effects of single dose calcium gluconate infusion in hypocalcemic preterm infants (Porcelli, Jr., 1995)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
</tr>
</tbody>
</table>
| **Population Demographics** | • 22 preterm neonates within 72 hours from birth (gestational ages: 24 – 35 weeks)  
  • Subjects were randomized to calcium gluconate group (n = 22, and 11/22 were symptomatic) or placebo group (n = 21, and 12/21 were symptomatic)  
  • Exclusion criteria: (1) prenatal maternal magnesium therapy; (2) suspected disorders of maternal or infant calcium metabolism, such as parathyroid disease; (3) infant blood transfusion; (4) infant calcium administration for medical indications, such as hyperkalemia. |
| **Hypocalcemia** | Hypocalcemia definition: Total serum calcium < 7.0 mg/dL (1.75 mmol/L).  
  Symptomatic hypocalcemia: irritability, jitteriness, and twitching were scored (scale 0 – 9) by blinded observers.  
  The infant was assessed by blinded nursing and medical personnel for signs consistent with hypocalcemia and assigned a hypocalcemic sign score of 0: none, 1: mild, 2: moderate, and 3: severe each for twitching, irritability, and jitteriness. Jitteriness was defined as rapid, short (less than 2 seconds) reciprocate muscle activity, most often in the extremities. Twitching was defined as slower, longer range movements with a contraction/relaxation phase lasting longer than 2 seconds. Irritability was assessed by the degree of agitation, vigor of crying, and ease of satiety or comfort. The maximum total sign score was 9. |
| **Treatment (per arm)** | • Treatment arm: A single IV bolus dose of 100 mg/kg (1 mL/kg of calcium gluconate 10%) over 30 to 60 minutes  
  • Placebo arm: normal saline solution |
| **Assessment** | Serum total, ionized calcium and hypocalcemic sign score were assessed before and 3 to 6 hours following the administration of calcium gluconate or placebo |
**Study Title:** Effects of single dose calcium gluconate infusion in hypocalcemic preterm infants (Porcelli, Jr., 1995)

<table>
<thead>
<tr>
<th>Endpoints and related definitions</th>
<th>Endpoints were the changes in total and ionized serum calcium, scores for hypocalcemic signs (irritability, jitteriness, and twitching)</th>
</tr>
</thead>
</table>
| **Efficacy results related to calcium gluconate**          | • Calcium gluconate arm: Total serum calcium increased from 1.58 ± 0.03 to 1.70 ± 0.05 mmol/L (p = 0.001) and ionized calcium increased from 0.67 ± 0.03 to 0.80 ± 0.02 mmol/L (p = 0.002) following calcium administration.  
  • Placebo arm: Neither total nor ionized serum calcium concentrations changed in the placebo group.  
  • Of the infants with hypocalcemic signs, the average score of hypocalcemic signs decreased in 11/11 calcium-treated infants (mean score decreased from 2.1 ± 0.5 to 0.9 ± 0.2 [p= 0.03]). No significant changes were observed in 12/12 infants in the control group. |

| Safety Data | Not reported |

Reference ID: 4055037
### 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)*

<table>
<thead>
<tr>
<th>Location</th>
<th>USA (St. Louis Children’s Hospital)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>Randomized controlled</td>
</tr>
<tr>
<td><strong>Population Demographics</strong></td>
<td>18 neonates with early neonatal hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>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 &lt; 2.5 mg/mL the subjects were randomized to either IV bolus or IV drip group:</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: not reported</td>
</tr>
</tbody>
</table>

**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: Treatment of early-onset neonatal hypocalcemia. Effects on serum calcium and ionized calcium

**Study Title:** Treatment of early-onset neonatal hypocalcemia. Effects on serum calcium and ionized calcium (*Brown, 1981*)

<table>
<thead>
<tr>
<th>Location</th>
<th>USA (Magee-Womens Hospital, Pittsburgh)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>Randomized, placebo controlled</td>
</tr>
</tbody>
</table>

**Population Demographics**
- 36 neonates admitted to the intensive care nursery
- Subjects were randomized to 1 of 3 groups: high dose (n=18), low dose (n=18) or no parenteral calcium treatment (n= 11)
- Exclusion criteria: all subjects were studied for 72 hours after entering the study unless died or were withdrawn because of treatment failure. Treatment failure was defined as parenteral calcium in excess of that prescribed by the study protocol was required to treat a serum calcium of < 5.0 mg/dL, extreme jitteriness, tetany or seizures, or when calcium was given as part of cardiopulmonary resuscitation.

**Hypocalcemia**
- Hypocalcemia definition: Total serum calcium < 7.0 mg/dL (1.75 mmol/L).
- Symptomatic hypocalcemia: Only 1 patient had ionized calcium < 2.5 mg/mL. The patient was symptomatic (jitteriness)

**Treatment (per arm)**
- **High dose:** Group H: 600 mg/kg/24 hours followed by 300 mg/kg/24 hours of calcium gluconate 10%. Subjects were treated either as a continuous infusion (Group C: high dose/continuous infusion [HC], n = 9) or by intermittent injection over a period of 1 to 2 minutes, and every 6 hours (120 – 150 mg/dose for first 24 hours and 60 – 75 mg/dose for the following 24 hours) (Group I: high dose/intermittent injection [HI], n = 9). Calcium gluconate (9% elemental calcium) was given through a peripheral vein or an umbilical arterial catheter
- **Low dose:** Group L: 200 mg/kg/24 hours followed by 100 mg/kg/24 hours of calcium gluconate 10%. Subjects were treated either as a continuous infusion (Group C: low dose/continuous infusion [LC], n = 10) or by intermittent injection over a period of 1 to 2 minutes, and every 6 hours (40 – 50 mg/dose for first 24 hours and 20 – 25 mg/dose for the following 24 hours) (Group I: low dose/intermittent injection [LI]: n = 8). Calcium gluconate (9% elemental calcium) was given through a peripheral vein or an umbilical arterial catheter
- **Controlled arm:** Group CON: no calcium was provided

**Assessment**
- Serum total, ionized calcium were assessed before the treatment and at 24, 48 and 72 hours following the administration of calcium gluconate or placebo.
### Study Title
Treatment of early-onset neonatal hypocalcemia. Effects on serum calcium and ionized calcium *(Brown, 1981)*

<table>
<thead>
<tr>
<th><strong>Endpoints and related definitions</strong></th>
<th>Endpoints were the efficacy of 2 different amount of parenteral calcium, given either continuously and intermittently for the treatment of early onset neonatal hypocalcemia</th>
</tr>
</thead>
</table>
| **Efficacy results related to calcium gluconate** | • After the first 24 hours of treatment, serum calcium increased in calcium-treated groups (both high and low dose) but not in the control group. In addition, Group H (both C and I) had statistically higher serum calcium concentrations than did Group CON.  
• During the entire 72-hour study period, group H had a lower incidence of hypocalcemia (22%) (serum calcium level < 7.0 mg/dL) when compared with all other patients (50% in group L and 55% in group CON) |
| **Safety Data** | Heart rate was monitored during bolus infusion. No morbidity from the infusion of calcium into either peripheral vein or umbilical catheter |
Study Synopsis: Reduction of adverse citrate reactions during autologous large-volume PBPC apheresis by continuous infusion of calcium-gluconate

<table>
<thead>
<tr>
<th>Study Title: Reduction of adverse citrate reactions during autologous large-volume PBPC apheresis by continuous infusion of calcium-gluconate (Buchta, 2003)</th>
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<tbody>
<tr>
<td><strong>Location</strong></td>
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<tr>
<td><strong>Study Design</strong></td>
</tr>
</tbody>
</table>
| **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 |

Reference ID: 4055037
**Study Synopsis:** A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children

<table>
<thead>
<tr>
<th><strong>Study Title:</strong> A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children (Broner, 1990)</th>
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</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
</tr>
</tbody>
</table>
| **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: Ionization and hemodynamic effects of calcium chloride and calcium gluconate in the absence of hepatic function**

**Study Title:** Ionization and hemodynamic effects of calcium chloride and calcium gluconate in the absence of hepatic function (*Martin, 1990*)

<table>
<thead>
<tr>
<th>Location</th>
<th>USA (Pittsburg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Randomized, active controlled</td>
</tr>
</tbody>
</table>

**Population Demographics**
- 7 patients (mean age 40 ± 11.8 years) with anhepatic stage during liver transplantation.
- Subjects were randomized to 2 groups: calcium gluconate (n = 7) or calcium chloride (n=8):
- Exclusion criteria: patients who developed hypocalcemia before or after anhepatic stage. Patients who required vasopressor support.

**Hypocalcemia**
Hypocalcemia: Ionized calcium < 0.8 mmol/L

**Treatment (per arm)**
- Calcium gluconate arm: a single dose of 30 mg/kg calcium gluconate 10% (~1800mg for a subject of 60 kg)
- Calcium chloride arm: a single dose of 10 mg/kg calcium chloride

**Assessment**
Arterial ionized calcium levels were assessed before and 30 seconds, 1 minute and 3, 5, 10 minutes after the treatment

**Endpoints and related definitions**
Endpoints were the changes in ionized serum calcium

**Efficacy results related to calcium gluconate**
- In calcium gluconate treated group, ionized serum calcium increased form 0.74 ± 0.11 to 1.05 ± 0.10 and 0.93 ± 0.10 and 0.89 ± 0.09 after 1, 5 and 10 minutes after the administration.
- The subjects with symptomatic hypocalcemia were not described. However, it is clear that some subject had predose serum ionized calcium levels ≤ 0.7 mmol/L (the threshold of symptomatic hypocalcemia (*French, 2012; Sorell, 1975*)). After 1 –10 minutes of calcium gluconate administration, it showed that all the subjects had serum ionized calcium above the threshold of symptomatic hypocalcemia.
- Equal ionized calcium concentration increased after the administration of either the salt forms.

**Safety Data**
No changes in cardiovascular function
5. REFERENCES


Approved Calcium Chloride Hospira Label.NDA 021117. Package insert for 10% Calcium Chloride Injection, USP. 2009. 4-25-2015.


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


Lambs L, Brion M, Berthon G. Metal ion-tetracycline interactions in biological fluids. Part 3. Formation of mixed-metal ternary complexes of tetracycline, oxytetracycline, doxycycline and minocycline with calcium and magnesium, and their involvement in the bioavailability of these antibiotics in blood plasma. Agents Actions 1984; 14(5-6):743-750.


Phebra Pty. Calcium Gluconate Injection 10mL Labeling, Australian Register of Therapeutic Goods ID 22923. 5-17-2013. 5-5-2015.

Reference ID: 4055037


Salix Pharms. Diuril: Chlorothiazide NDA 011870. 6-10-2009.


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

/s/

RENU SINGH
02/11/2017

JAYABHARATHI VAIDYANATHAN
02/11/2017
# Clinical Pharmacology Filing Form

## Application Information

<table>
<thead>
<tr>
<th>Application Information</th>
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<tbody>
<tr>
<td><strong>NDA/BLA Number</strong></td>
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<tr>
<td><strong>SDN</strong></td>
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<tr>
<td><strong>Applicant</strong></td>
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<tr>
<td><strong>Generic Name</strong></td>
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<tr>
<td><strong>Brand Name</strong></td>
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<tr>
<td><strong>Submission Date</strong></td>
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<tr>
<td><strong>Drug Class</strong></td>
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<tr>
<td><strong>Indication</strong></td>
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<tr>
<td><strong>Dosage Regimen</strong></td>
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<tr>
<td><strong>Dosage Form</strong></td>
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<tr>
<td><strong>Route of Administration</strong></td>
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<tr>
<td><strong>OCP Division</strong></td>
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<tr>
<td><strong>OND Division</strong></td>
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<tr>
<td><strong>OCP Review Team</strong></td>
</tr>
<tr>
<td><strong>Primary Reviewer(s)</strong></td>
</tr>
<tr>
<td><strong>Secondary Reviewer/ Team Leader</strong></td>
</tr>
<tr>
<td><strong>Pharmacometrics</strong></td>
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<td><strong>Genomics</strong></td>
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<tr>
<td><strong>Review Classification</strong></td>
</tr>
<tr>
<td><strong>Filing Date</strong></td>
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<tr>
<td><strong>74-Day Letter Date</strong></td>
</tr>
<tr>
<td><strong>Review Due Date</strong></td>
</tr>
<tr>
<td><strong>PDUFA Goal Date</strong></td>
</tr>
</tbody>
</table>

## Application Fileability

**Is the Clinical Pharmacology section of the application fileable?**

☑ Yes

☐ No

If no list reason(s)

**Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?**

☐ Yes

☑ No

If yes list comment(s)

**Is there a need for clinical trial(s) inspection?**

☐ Yes

☑ No

If yes explain:

---

## Clinical Pharmacology Package

- Tabular Listing of All Human Studies: ☑ Yes
- Clinical Pharmacology Summary: ☑ Yes
- Bioanalytical and Analytical Methods: ☑ Yes
- Labeling: ☑ Yes

## Clinical Pharmacology Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Count</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Vitro Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism Characterization</td>
<td></td>
<td>Literature based application. No non clinical studies conducted by the sponsor.</td>
</tr>
<tr>
<td>Transporter Characterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-Drug Interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Vivo Studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Reference ID: 3956611
### Biopharmaceutics
- □ Absolute Bioavailability  
  Literature based application. No clinical studies conducted by the sponsor.
- □ Relative Bioavailability
- □ Bioequivalence
- □ Food Effect
- □ Other

### Human Pharmacokinetics
- □ Healthy Subjects  
  □ Single Dose
  □ Multiple Dose
- □ Patients  
  □ Single Dose
  □ Multiple Dose
- □ Mass Balance Study
- □ Other (e.g. dose proportionality)

### Intrinsic Factors
- □ Race
- □ Sex
- □ Geriatrics
- □ Pediatrics
- □ Hepatic Impairment
- □ Renal Impairment
- □ Genetics

### Extrinsic Factors
- □ Effects on Primary Drug
- □ Effects of Primary Drug

### Pharmacodynamics
- □ Healthy Subjects
- □ Patients

### Pharmacokinetics/Pharmacodynamics
- □ Healthy Subjects
- □ Patients
- □ QT

### Pharmacometrics
- □ Population Pharmacokinetics
- □ Exposure-Efficacy
- □ Exposure-Safety

### Total Number of Studies
- Total Number of Studies to be Reviewed
  - In Vitro 0
  - Literature reference
  - In Vivo 0
  - Literature reference

---

### Criteria for Refusal to File (RTF)

<table>
<thead>
<tr>
<th>RTF Parameter</th>
<th>Assessment</th>
<th>Comments</th>
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<tbody>
<tr>
<td>1. Did the applicant submit bioequivalence data</td>
<td>□Yes □No □N/A</td>
<td>505(b)(2) application with bio-waiver request submitted</td>
</tr>
<tr>
<td>Question</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----</td>
<td>----</td>
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<tr>
<td>2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td>3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td>4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?</td>
<td></td>
<td>☑</td>
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<tr>
<td>5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?</td>
<td></td>
<td>☑</td>
</tr>
<tr>
<td>6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td>7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?</td>
<td></td>
<td>☑</td>
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<tr>
<td>8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td>9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?</td>
<td>☑</td>
<td></td>
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<tr>
<td><strong>Complete Application</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is ‘No’, has the sponsor submitted a justification that was previously agreed to before the NDA submission?</td>
<td>☑</td>
<td></td>
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**Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist**

**Data**

1. Are the data sets, as requested during pre-submission discussions, submitted in the

   ☑ Yes ☑ No ☑ N/A
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
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<tr>
<td><strong>Studies and Analysis</strong></td>
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<tr>
<td>3. Is the appropriate pharmacokinetic information submitted?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
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<tr>
<td>5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?</td>
<td>☑</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
</tbody>
</table>
Overview

- Type of Submission:
  - 505(b)(2) – literature based

- Proposed Indications:
  - [Redacted]

- Formulation:
  - Calcium Gluconate Injection, USP
  - sterile, nonpyrogenic, supersaturated solution

- Administration:
  - Intravenous

- Proposed dose:
  - The dose ranges from 29 mg/kg/dose to 54 mg/kg/dose

Background

- The Sponsor markets Calcium Gluconate Injection, USP 10% which is currently an unapproved drug.

- FK USA intends to rely on the clinical and nonclinical data contained in the peer reviewed scientific literature to support the approval of its proposed product.

- 6 pivotal studies involving 128 patients with symptomatic or asymptomatic hypocalcemia and 62 supportive efficacy studies involving 1311 subjects were used to support efficacy of calcium gluconate for IV use.

- For safety analysis, 150 studies involving 3298 subjects were identified.

Clinical Pharmacology

Pharmacokinetics

Absorption: Bioavailability 100%

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% to 10% serum calcium is bound to organic and inorganic acid and approximately 40% is protein-bound (primarily to albumin).

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%.
Clinical Pharmacology

Drug-drug interactions

- **Cardiac glycosides**: Synergistic arrhythmias may occur if calcium and cardiac glycosides are administered together. Intravenous administration of calcium should be avoided in patients receiving cardiac glycosides; if considered necessary, calcium should be given slowly in small amounts and close ECG monitoring is recommended.

- **Ceftriaxone**: Concurrent use of iv ceftriaxone and calcium-containing solutions may cause life-threatening adverse drug reactions due to the formation of ceftriaxone-calcium precipitates. Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions via a Y-site in any age group [see Warnings and Precautions (5.2)].

Clinical Pharmacology

Drug-drug interactions

- **Vitamin D**: Vitamin D increases the gastrointestinal absorption of calcium (e.g., from dietary sources). High vitamin D intake should be avoided during calcium therapy unless especially indicated.

- **Calcium channel blockers**: Administration of calcium may reduce the response to calcium channel blockers.

- **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.

Clinical Pharmacology

Drug-drug interactions

- **Phosphate and bicarbonate**: Calcium should not be mixed with fluids containing phosphate or bicarbonate to avoid precipitation.

Not reported: Interactions with ciprofloxacin, phenytoin, neuromuscular blockers, levothyroxine, iron preparations, multivitamins and alendronate.
Clinical Pharmacology

Dose recommendations in Special population:

- **Hepatic impairment**: Dose adjustment in hepatically impaired patients may not be necessary, however the total dose is dependent upon the serum calcium level of patients.

- **Renal impairment**

  Monitoring serum calcium levels every 4 hours is also recommended.

Review Focus

- Are the claims made in the label supported by the literature?

- Are the pivotal studies robust enough to support the claims?
  - Study design
  - Doses used
  - Bioanalytical methods

- Are there any additional important data not reported by the sponsor?

Filing Status and Consults

- Clin Pharm recommends NDA 208418 to be fileable because:
  - Dosing in adults, pediatrics and neonates, PK and drug-drug interaction information is provided and references cross listed
  - Bioanalytical analysis was performed for few of the pivotal studies
  - Proposed product labeling provided

- No PK studies submitted. Bio-waiver request submitted by the sponsor.

- OSIS consult:
  - None

- Request for Sponsor:
  - None
### Filing Memo

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

- ☑ Yes  ☐ No

If the NDA/BLA is not fileable from the clinical pharmacology 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.

**Comments to Sponsor:** None

<table>
<thead>
<tr>
<th>Renu Singh</th>
<th>8 July, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewing Clinical Pharmacologist</td>
<td>Date</td>
</tr>
<tr>
<td>Jayabharathi Vaidyanathan</td>
<td>8 July, 2016</td>
</tr>
<tr>
<td>Team Leader</td>
<td>Date</td>
</tr>
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</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENU SINGH
07/08/2016

JAYABHARATHI VAIDYANATHAN
07/08/2016