CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 210906
Supporting document/s:	SDN1, SN0000
Applicant's letter date:	09/29/2017
CDER stamp date:	09/29/2017
Product:	Calcium Gluconate Injection, 1 g/50 mL and 2 g/100 mL (20 mg/mL)
Indication:	Acute treatment of symptomatic hypocalcemia
Applicant:	HQ Specialty Pharma Corporation
Review Division:	Division of Metabolism and Endocrine Products
Reviewer:	Arulasanam K. Thilagar, Ph.D.
Supervisor/Team Leader:	C. Lee Elmore, Ph.D.
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Disclaimer

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1 Executive Summary

1.1 Introduction

HQ Specialty Pharma Corporation (the "Applicant") seeks approval to market Calcium Gluconate Injection via the 505(b)(2) regulatory pathway through reliance on FDA's prior findings of safety and efficacy for the approved drug, Calcium Gluconate Injection, USP 10% (Fresenius Kabi; NDA 208418) as listed in the FDA Orange Book, hereafter referred to as the "listed drug" or "LD".

Calcium Gluconate Injection is intended for the treatment of acute, symptomatic hypocalcemia and is available in 1000 mg/per 50 mL or 2000 mg per 100 mL single use (b) (4) bags. Each milliliter of Calcium Gluconate Injection contains 20 mg of calcium gluconate (18.8 mg of calcium gluconate and 0.9 mg of calcium D-saccharate tetrahydrate), 6.75 mg/mL sodium chloride, hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 6.0 to 8.2). The required clinical dose is dependent upon the serum calcium levels of individual patients. The route of administration and dosing regimen (dose, frequency, and duration) for the Applicant's premixed Calcium Gluconate Injection product is similar to that of the listed drug's, once the LD is diluted for administration.

1.2 Brief Discussion of Nonclinical Findings

Mechanism of Action, Metabolism and General Toxicity

Many vital cellular biological processes, such as blood coagulation, neuromuscular excitability, maintenance of cell membrane integrity, and cellular homeostasis are dependent on maintenance of adequate free ionized plasma calcium concentrations.

Calcium gluconate metabolism is limited to the gluconate component of the salt, as ionized calcium itself does not undergo direct metabolism. Gluconate is a normal product of glucose metabolism. The daily production of gluconate from endogenous sources is estimated to be about 450 mg for a 60 kg person, which amounts to 27 g or more than twice the estimated daily intake of gluconate from the proposed maximum dose (12 g) of Calcium Gluconate Injection for the treatment of hypocalcemia (American Societies for Experimental Biology (1975)).

The Applicant conducted no nonclinical studies to support the safety of Calcium Gluconate Injection and provided no literature references for the primary pharmacology, secondary pharmacology, safety pharmacology, pharmacokinetics, safety pharmacology, general toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity, or local tolerance. Instead, the Applicant seeks to rely upon the FDA's previous findings of safety and efficacy of the listed drug (NDA 208418) as the sole source of information to support this 505(b)(2) submission.

Calcium toxicity in laboratory animals is primarily due to hypercalcemia, including soft tissue mineralization, especially in the kidneys, hypercalciuria, nephropathy, weight loss (due to decreased food consumption), altered bone metabolism, decreased clotting

time, abnormal heart rhythms and neurologic effects. Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Calcium Gluconate Injection. Calcium gluconate was not mutagenic with or without metabolic activation in the Ames test with *Salmonella typhimurium*. No animal reproduction studies were conducted with the LD, but adequate calcium levels are expected to be required during pregnancy. Glucono-delta-lactone administration had no effect on implantation or on maternal or fetal survival in mice, rats, hamsters and rabbits.

Excipients

Calcium Gluconate Injection contains no novel excipients.

Impurities of Toxicological Concern

Calcium mineral (the mined source of calcium in Calcium Gluconate Injection) contains a variety of metal impurities, which may vary widely by source. The metal of toxicological concern in Calcium Gluconate Injection is aluminum. Aluminum is a potentially toxic to the CNS and bone with exposure by the intravenous route, especially in patients with poor renal function, including neonates. However, at the maximum recommended doses of Calcium Gluconate Injection, and based on the Applicant's proposed release specification for aluminum, the daily aluminum exposure will be below 4 mcg/kg/day, levels associated with central nervous system and bone toxicity in patients with impaired kidney function, including premature neonates. Tissue loading may occur at even lower rates of administration, but Calcium Gluconate for Injection is indicated only for acute use until calcium homeostasis is restored.

1.3 Recommendations

1.3.1 Approvability

This NDA is approvable from the Pharm/Tox perspective.

1.3.2 Additional Nonclinical Recommendations

The product labeling should clearly state the aluminum levels in Calcium Gluconate Injection, to inform the risk of off-label use for longer-term calcium administration (e.g., via total parenteral nutrition).

1.3.3 Labeling

Reviewer's Recommended Labeling:

INDICATIONS AND USAGE

Calcium Gluconate Injection is a form of calcium indicated for pediatric and adult patients for the treatment of acute symptomatic hypocalcemia.

Limitations of Use
The safety of Calcium Gluconate Injection for long term use has not been established.

5 WARNINGS AND PRECAUTIONS

5.5 Aluminum Toxicity

Calcium Gluconate Injection contains aluminum, up to 25 mcg per liter, that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 mcg/kg/day to 5 mcg/kg/day accumulate aluminum levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary (Nonclinical portion only)
No animal reproduction studies have been conducted with Calcium Gluconate Injection.

8.2 Lactation

Risk Summary (Nonclinical portion only)
[In the absence of animal data, no statement based on animals should be included.]

12 Clinical Pharmacology

12.1 Mechanism of Action

Intravenous administration of calcium gluconate increases serum ionized calcium level. Calcium gluconate dissociates into ionized calcium in plasma. Ionized calcium and gluconate are (b) (4) constituents of body fluids.

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Calcium Gluconate Injection. Calcium gluconate was not mutagenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* (strains TA-1535, TA-1537, and TA-1538) or *Saccharomyces cerevisiae* (Strain D4). Fertility studies in animals have not been conducted with calcium gluconate administered by the intravenous route.

2 Drug

2.1 Drug identity

Name
Calcium Gluconate Injection, 1 g/50 mL and 2 g/100 mL (20 mg/mL)

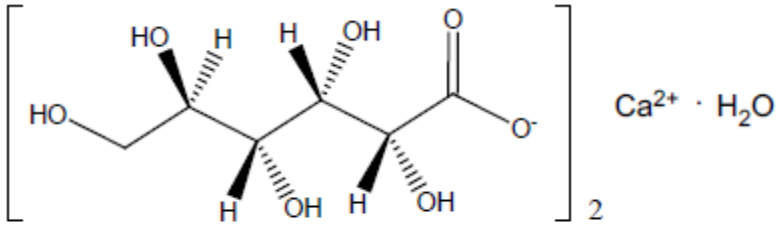
CAS Registry Number
18016-24-5

Generic Name
Calcium gluconate

Chemical Name
Calcium gluconate monohydrate

Molecular Formula/Molecular Weight
$C_{12}H_{22}CaO_{14}\cdot H_2O$ / 448.39

Structure or Biochemical Description



Pharmacologic Class
Calcium

Manufacturer of API
(b) (4)

Letter of Authorizations from Manufacturer of API
Provided in the Appendix - DMF Type II (b) (4)

Manufacturer of Calcium Gluconate Injections (1 g/50mL and 2 g/100mL)
(b) (4)
(b) (4) received a satisfactory FDA inspection August 8th -16th, 2016. A copy of the FDA cGMP acceptability letter is included (see Appendix). Also included, is a copy of cGMP certification for (b) (4)

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 208418 - Calcium Gluconate Injection, USP 10%
DMF (b) (4)

2.2 Drug Formulation

The components and composition of the final drug product and the function of each excipient are given below.

Table 1: Components of Calcium Gluconate Injection

Name of Ingredients	Grade	Function
Calcium Gluconate	USP	Active Ingredient
Calcium D-Saccharate (tetrahydrate)	USP	(b) (4)
HCl/NaOH	NF	
Sodium Chloride	USP	Tonicity Agent
(b) (4)		

Table 2: Composition of Calcium Gluconate Injection (1 g/50 mL)

Name of Ingredients	Composition	
	Amount per mL (mg)	**Amount per 50 mL (mg)**
Calcium Gluconate Monohydrate (b) (4)	(b) (4) (18.8)	(b) (4) (940)
Calcium D-Saccharate (tetrahydrate)	0.9	45
HCl/NaOH	qs	qs
Sodium Chloride	6.75	337.5
(b) (4)		
Total Volume	**1 mL**	**50 mL**

Table 3: Composition of Calcium Gluconate Injection (2 g/100 mL)

Name of Ingredients	Composition	
	Amount per mL (mg)	**Amount per 100 mL (mg)**
Calcium Gluconate Monohydrate (b) (4)	(b) (4) (18.8)	(b) (4) (1880)
Calcium D-Saccharate (tetrahydrate)	0.9	90
HCl/NaOH	qs	qs
Sodium Chloride	6.75	675
(b) (4)		
Total Volume	**1 mL**	**100 mL**

Description of Dosage Form

Calcium Gluconate Injection, 1 g/50 mL and 2 g/100 mL (20 mg/mL) is a ready to infuse solution in (b) (4) bags. The drug product is stored at room temperature (b) (4)

2.3 Container Closure System

Calcium Gluconate Injection, 1 g/50 mL and 2 g/100 mL (20 mg/mL) is packaged in single use 100 mL bags (b) (4), containing a pre-printed label. The bags contain a single port. The bags are placed in a (b) (4) aluminum overwrap with pre-printed labels using green and blue and black ink. The bags are made of (b) (4) .

The Applicant provided a summary of components used in container closure system and the manufacturers/suppliers and DMF numbers.

Table 4: Description of the Container Closure System

Description of the Container Closure System				
Container Closure System	**Component**	**Raw Material Supplier**	**Supplier**	**DMF number**
(b) (4) 100 mL bags (b) (4)	(b) (4) 100 mL bag, (b) (4)			(b) (4)
Port: Twist off port				
Overwrap	Each bag is over-wrapped (b) (4) Aluminium (b) (4)		(b) (4)	Not available*
nk	Pigment Ink			(b) (4)

*Component does not contact the drug material and therefore does not require a DMF.

Note: the container closure system is used (b) (4)

(b) (4)

The compatibility of the product with the excipients and packaging material has been evaluated during the stability studies performed at normal and accelerated conditions and the results obtained have shown that the product is stable and therefore a shelf life of 24 months is proposed. Applicant stated that the stability studies will continue until 36 months (b) (4)

2.4 Comments on Novel Excipients

No novel excipients are used in the manufacture of Calcium Gluconate Injection. The excipients contained in Calcium Gluconate Injection, 1 g/ 50 mL and 2 g/ 100 mL (20 mg/mL) are listed in the Table below.

Table 5: Excipients in Drug Product

Excipients	Quantity (mg/mL)	Function
Calcium D-Saccharate (tetrahydrate)	0.9	(b) (4)
Sodium Chloride	6.75	Tonicity agent
Hydrochloric Acid	qs to pH	pH adjuster
Sodium Hydroxide	qs to pH	pH adjuster
(b) (4)		

Calcium D-saccharate, sodium hydroxide and hydrochloric acid are present in the Listed Drug's concentrate formulation. (b) (4)

Glucarate is transported in the blood to a number of different organs in Sprague-Dawley rats

(Walaszek, 1997). Hydrochloric acid and sodium hydroxide are listed in FDA's IIG list for intravenous use. The amounts of these excipients are low as they are only used for pH adjustment.

2.5 Comments on Impurities/Degradants of Concern

No organic impurities were noted in the Calcium Gluconate Monohydrate impurity profile. No Class 1, Class 2 or Class 3 solvents are used in the manufacture of Calcium Gluconate Monohydrate. Therefore, there is no solvents are present in Calcium Gluconate Monohydrate. (b) (4)

(b) (4)

The Applicant is using the calcium gluconate from a supplier, (b) (4)

There are no safety concerns from the additional impurities originating from the excipients used.

Calcium D-saccharate is present in Calcium Gluconate Injection. (b) (4)

(b) (4)

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2.6 Proposed Clinical Population and Dosing Regimen

Calcium Gluconate Injection is a form of calcium indicated for pediatric and adult patients for the treatment of acute symptomatic hypocalcemia. The dose of Calcium Gluconate Injection is dependent on the requirements of the individual patient. Calcium Gluconate Injection is provided in ready-to-use formulations for intravenous administration to infants, pediatric and adult patients. Calcium Gluconate Injection is a solution available in single use bags with aluminum overwrap for injection. Each mL of Calcium Gluconate Injection contains 1.86 mg (0.093 mEq) of elemental calcium.

Table 14: Dosing Recommendations in mg of Calcium Gluconate for Neonate, Pediatric, and Adult Patients

Patient Population	Initial Dose	Subsequent Doses (if needed)	
		Bolus	Continuous
Neonate (≤ 1 month)	100 – 200 mg/kg	100 – 200 mg/kg every 6 hours	Initiate at 17-33 mg/kg/hour
Pediatric (> 1 month to < 17 years)	29 - 60 mg/kg	29 – 60 mg/kg every 6 hours	Initiate at 8-13 mg/kg/hour
Adult	1000 - 2000 mg	1000 – 2000 mg (b) (4) every 6 hours	Initiate at 5.4 - 21.5 mg/kg/hour
For bolus administration, DO NOT exceed an infusion rate of: •200 mg/minute in adult patients •100 mg/minute in pediatric patients For continuous infusions, adjust rate as needed based on serum calcium levels			

The proposed clinical labeling recommends the following dosage in pregnant woman

Limited available data with Calcium Gluconate Injection use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. There are risks to the mother and the fetus associated with hypocalcemia in pregnancy. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S., general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

The proposed clinical labeling recommends the following dosage in neonates and pediatric patients:

Infants born to mothers with hypocalcemia can have associated fetal and neonatal hyperparathyroidism, which in turn can cause fetal and neonatal skeletal demineralization, subperiosteal bone resorption, osteitis fibrosa cystica and neonatal seizures. Infants born to mothers with hypocalcemia should be carefully monitored for signs of hypocalcemia or hypercalcemia, including neuromuscular irritability, apnea, cyanosis and cardiac rhythm disorders.

The safety and effectiveness of Calcium Gluconate Injection have been established in pediatric patients for the treatment of acute, symptomatic hypocalcemia. Pediatric approval for Calcium Gluconate Injection, including doses, is not based on adequate and well-controlled clinical studies. Safety and dosing recommendations in pediatric patients are based on published literature and clinical experience.

Concomitant use of ceftriaxone and Calcium Gluconate Injection is contraindicated in neonates (28 days of age or younger) due to reports of fatal outcomes associated with the presence of lung and kidney ceftriaxone-calcium precipitates. In patients, older than 28 days of age, ceftriaxone and Calcium Gluconate Injection may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.

The proposed label recommends the following dosage in geriatric, renal impairment and Hepatic impairment patients:

In general dose selection for an elderly patient should start at the lowest dose of the recommended dose range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

For patients with renal impairment, initiate Calcium Gluconate Injection at the lowest dose of the recommended dose ranges across all age groups. Monitor serum calcium levels every 4 hours

Hepatic function does not impact the availability of ionized calcium after calcium gluconate intravenous administration. Dose adjustment in hepatically impaired patients may not be necessary.

2.7 Regulatory Background

The Applicant submitted NDA 210906 for Calcium Gluconate Injection 1 g/50 mL and 2 g/100 mL (20 mg/mL) under section 505(b)(2) pathway. The filing is based upon the Orange Book listed drug (LD) Calcium Gluconate Injection (NDA 208418). The holder of the NDA 208418 is Fresenius Kabi.

The calcium gluconate API is manufactured by (b) (4) The applicant provided a letter authorizing FDA to reference (b) (4) Type II DMF (b) (4)

The Applicant submitted NDA 210906 on September 29, 2017. No IND related to this submission was noted. The Applicant submitted a full waiver for the Initial Pediatric Study Plan (iPSP) on October 4, 2017.

The applicant submitted an amendment on October 30, 2017 in response to the Information Request dated October 26, 2017 from FDA. The Applicant submitted Patent Certification (Form 3542a) on December 30, 2017. The Applicant submitted a response on December 15, 2017 to FDA Information Request dated November 15,

2017. The Applicant submitted a response on February 5, 2018 to FDA Information Request dated January 4, 2018. The Applicant submitted an Amendment (updated 356 H). This Amendment was to correct the LD application number. The Applicant submitted a response on March 23, 2018 to FDA Information Request dated February 22, 2018. The Applicant submitted a response on April 5, 2018 to FDA Information Request dated March 30, 2018.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical studies have been conducted by the Applicant. The Applicant relies solely on the FDA's previous findings of safety and efficacy for NDA 208418 to support its 505(b)(2) submission.

The route of administration and dosing regimen (dose, frequency, and duration) for the Applicant's premixed Calcium Gluconate Injection product are the same as the listed drug's.

4 Integrated Summary and Safety Evaluation

The Applicant filed this NDA to market Calcium Gluconate Injection via the 505(b)(2) regulatory pathway. Calcium Gluconate Injection is intended for the treatment of acute, symptomatic hypocalcemia. The Applicant conducted no nonclinical studies or provided, literature references for the primary pharmacology, secondary pharmacology, safety pharmacology, pharmacokinetics, safety pharmacology, general toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, or other toxicities. The Applicant relies on the FDA's previous findings of safety and efficacy of the approved drug, Calcium Gluconate Injection, USP 10% (NDA 208418) as the sole source to support this 505(b)(2) submission. The route of administration and dosing regimen (dose, frequency, and duration) for the Applicant's premixed Calcium Gluconate Injection product will be same as the Calcium Gluconate Injection listed drug's once the LD is diluted.

Calcium Gluconate Injection is available as 1000 mg/per 50 mL (18.8 mg/mL) or 2000 mg per 100 mL single use, (b) (4) bags with aluminum overwrap. Each 1 mL of Calcium Gluconate Injection contains 20 mg of calcium gluconate (equivalent to 18.8 mg of calcium gluconate and 0.9 mg of calcium D-saccharate tetrahydrate), 6.75 mg/mL sodium chloride, hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 6.0 to 8.2). The materials used for forming the bags comply with the US Pharmacopoeia, current edition, and with the FDA – Regulation 21 CFR 201.56. The container closure system (b) (4)

Calcium is the major extracellular divalent cation in mammals. More than 95% of total physiologic calcium is located within osseous tissues and the remaining amount of

physiologic calcium is present in small amounts in extracellular fluids and to a minor extent within cells. In the plasma, about 45% of ionized calcium is protein bound, primarily to albumin, with about 10% being complexed with anionic buffers, such as citrate and phosphate. The remaining fraction of “free” ionized calcium is the component that exerts physiological effects. Reduction of calcium below normal levels results in the manifestation of overt hypocalcemia symptoms. Many vital cellular biological processes, as well as cell membrane integrity and cell function, are known to be dependent upon maintenance of adequate ionized plasma calcium concentrations (Jain, 2010; Zaloga, 1992).

Under normal physiologic conditions, extracellular calcium levels are regulated by endocrine control; which affects calcium uptake at the level of the intestine and ultimate excretion at the level of the kidney with secondary renal associated regulation of compartmentalized calcium (within osseous tissues) enabling calcium release from sequestered stores in times of physiological need (Zaloga, 1992). Significant amounts of calcium are secreted in milk during lactation in mammals post-parturition.

The extracellular calcium concentration has three primary regulators: Calcium-sensing receptor (CaSR), parathyroid hormone (PTH), and vitamin D. The CaSR is a membrane-bound receptor found in multiple tissues, including cells of the parathyroid glands. When plasma ionized calcium concentrations are sufficient to stimulate the CaSR, the result is inhibited PTH release. When the ionized calcium concentration is low, PTH is released and is carried in blood to its target tissues: bone and kidney (Zhou, 2009). Intravenous administration of calcium gluconate in combination with Vitamin D has been observed to significantly increase bone mineralization in rabbits (Lani, 2014).
Intravenous administration of calcium gluconate increases serum ionized calcium level. Calcium gluconate dissociates into ionized calcium in plasma. Ionized calcium and gluconate are normal constituents of body fluids. Information on the toxicity of calcium gluconate in the literature show that calcium toxicity is associated with hypercalcemia in laboratory animals, consisting of soft tissue mineralization, especially in the kidneys, hypercalciuria, nephropathy, weight loss (due to decreased food consumption), altered bone metabolism, decreased clotting time, abnormal heart rhythms and altered behavior (i.e., neurologic effects).

The mutagenic potential of calcium gluconate has been evaluated and Calcium gluconate has been shown to be negative in mutagenicity assays conducted in bacteria and yeast. Calcium Gluconate Injection has not been evaluated in lifetime rodent carcinogenicity studies. Glucono-delta-lactone (a neutral cyclic ester of gluconic acid in equilibrium with gluconic acid in solution) did not induce compound-related tumors in a 2-year feeding study in rats. No animal reproduction studies were conducted with Calcium Gluconate Injection. Adequate calcium levels are expected to be beneficial during pregnancy. Glucono-delta-lactone administration had no effect on implantation or on maternal or fetal survival in mice, rats, hamsters and rabbits.

No novel excipients are used in the manufacture of Calcium Gluconate Injection. Calcium D-saccharate, sodium hydroxide and hydrochloric acid are present in the Listed

Drug's concentrate formulation. Calcium saccharate is listed in the USP monograph for Calcium Gluconate Injection, USP. The Sodium Chloride, USP, Hydrochloric Acid 37%, NF, and Sodium Hydroxide, NF used in the drug product comply with current USP/NF compendia requirements. Hydrochloric acid and sodium hydroxide are listed in FDA's IIG list for intravenous use. The amounts of these excipients are low as they are only used for pH adjustment. Sodium chloride used for manufacture Calcium Gluconate Injection meets pharmacopeia requirements (USP and Ph. Eur. Monograph) with associated elemental impurities limits. No metal catalyst or reagents are added intentionally to sodium chloride.

No organic impurities were noted in the Calcium Gluconate Monohydrate drug substance impurity profile.

Calcium D-saccharate is present in Calcium Gluconate Injection. (b) (4)

(b) (4)

CFR21 part 201 subpart 201-323 specifies that the amount of aluminum for small volume parenteral drug products shall be stated in product labeling. The Applicant analyzed elemental impurities in in six batches of Calcium Gluconate injections. The aluminum levels in these six batches were (b) (4) mcg/mL. (b) (4)

Premature neonates are particularly at risk of aluminum toxicity because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. At the maximum recommended dose of Calcium Gluconate Injection, the aluminum exposure will be less than 4 mcg/kg/day.

Oral calcium acetate, indicated for reduction of serum phosphorus in patients with end-stage renal disease (NDA 022581) and 10% Calcium Chloride Injection for the treatment of hypocalcemia (NDA 021117) are U.S. approved calcium containing products.

Calcium gluconate metabolism is limited to the gluconate component of the salt as ionized calcium itself does not undergo direct metabolism. As in humans, gluconate is a normal product of glucose metabolism in the rat and 60-85% of parenterally administered gluconate is excreted unchanged in the urine via tubular secretion.

Pharmacodynamic drug interactions are possible between calcium (calcium gluconate) and various other drug products, including but not limited to: digoxin, verapamil, aminoglycosides, and tetracycline antibiotics.

The Federation of American Societies for Experimental Biology (FASEB), Life Sciences Research Office and FAO/WHO Expert Committee on Food Additives (JECFA) discussed the toxicity profile of Calcium Gluconate. These reports are summarized in a GRAS Notification for (oral) Calcium Gluconate as a Food Supplement and the subsequent FDA Response to the GRAS notice. However, it is noted that the intended route of the Calcium Gluconate Injection, is intravenous, not oral. FASEB concluded that "Evidence suggests that any possible toxicity of gluconate salts is a function of the cation rather than of the gluconate portion of these substances."

Calcium Gluconate Injection is intended for the treatment of acute, symptomatic hypocalcemia and not for chronic dosing. This NDA is recommended for approval for the proposed indication provided the CMC approves the Applicant's Method of Analysis for aluminum and verifies the Applicant's product can be manufactured to meet the specified lower aluminum limit of (b) (4) µg/L.

5 Literature Citations

TITLE 21--FOOD AND DRUGS
Sec. 201.323 Aluminum in large and small volume parenteral used in total parenteral nutrition.

FASEB, (1975). EVALUATION OF THE HEALTH ASPECTS OF CERTAIN CALCIUM SALTS AS FOOD INGREDIENTS - Prepared for Bureau of Foods Food and Drug Administration Department of Health, Education, and Welfare Washington. D. C. Contract No. FDA 223-75-2004; Life Sciences Research Office Federation of American Societies for Experimental Biology 9650 Rockville Pike, Bethesda. Maryland 20014.

Federation of American Societies for Experimental Biology (FASEB), Life Sciences Research Office and the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

Fong, et al. (2012) Hypocalcemia-Updates in diagnosis and management for primary care. Canadian Family Physician • Le Médecin de famille canadien | Vol 58: FEBRUARY • FÉVRIER 2012.

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Walaszek, et al. (1997). Metabolism, Uptake, and Excretion of a D-Glucaric Acid Salt and Its Potential Use in Cancer Prevention. Cancer Detection and Prevention, 21(2):178-190 (1997).

WHO, (1999). SAFETY EVALUATION OF CERTAIN FOOD ADDITIVES- WHO FOOD ADDITIVES SERIES: 42- GLUCONO-delta-LACTONE AND THE CALCIUM, MAGNESIUM, POTASSIUM, AND SODIUM SALTS OF GLUCONIC ACID - First draft prepared by Dr C. Whiteside and Dr M. Bonner, Division of Health Effects Evaluation, Office of Premarket Approval, Center for Food Safety and Applied Nutrition, Food and Drug Administration Washington DC, USA.

Zaloga, (1992). Hypocalcemia in critically ill patients. Critical Care Medicine; Vol 20. No.2

Zhou, et al. (2009). Hypocalcemia in Infants and Children. Pediatrics in Review Vol.30 No.5 May 2009.

6 Applicant Suggested Labeling

INDICATIONS AND USAGE

- Calcium Gluconate Injection is a form of calcium indicated for pediatric and adult patients for the treatment of acute symptomatic hypocalcemia. (1)
- Limitations of Use: The safety of Calcium Gluconate Injection for long term use has not been established. (1)

5 WARNINGS AND PRECAUTIONS

5.5 Aluminum Toxicity

Calcium Gluconate Injection contains aluminum, up to 25 mcg per liter, that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 mcg/kg/day to 5 mcg/kg/day accumulate aluminum levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

8.1 Pregnancy

Risk summary

Limited available data with Calcium Gluconate Injection use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. There are risks to the mother and the fetus associated with hypocalcemia in pregnancy *[see Clinical Considerations]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal risk

Maternal hypocalcemia can result in an increased rate of spontaneous abortion, premature and dysfunctional labor, and possibly preeclampsia.

Fetal/Neonatal adverse reactions

Infants born to mothers with hypocalcemia can have associated fetal and neonatal hyperparathyroidism, which in turn can cause fetal and neonatal skeletal demineralization, subperiosteal bone resorption, osteitis fibrosa cystica and neonatal seizures. Infants born to mothers with hypocalcemia should be carefully monitored for signs of hypocalcemia or hypercalcemia, including neuromuscular irritability, apnea, cyanosis and cardiac rhythm disorders.

8.2 Lactation

Risk summary

Calcium is present in human milk as a natural component of human milk. It is not known whether intravenous administration of Calcium Gluconate Injection can alter calcium concentration in human milk. There are no data on the effects of Calcium Gluconate Injection on the breastfed infant, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Calcium Gluconate Injection and any potential adverse effects on the breastfed child from Calcium Gluconate Injection or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Calcium Gluconate Injection have been established in pediatric patients for the treatment of acute, symptomatic hypocalcemia. Pediatric approval for Calcium Gluconate Injection, including doses, is not based on adequate and well-controlled clinical studies. Safety and dosing recommendations in pediatric patients are based on published literature and clinical experience *[see Dosage and Administration (2.2)]*.

Concomitant use of ceftriaxone and Calcium Gluconate Injection is contraindicated in neonates (28 days of age or younger) due to reports of fatal outcomes associated with the presence of lung and kidney ceftriaxone-calcium precipitates. In patients older than 28 days of age, ceftriaxone and Calcium Gluconate Injection may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid [*see Contraindications (4) and Warnings and Precautions (5.2)]*. This product contains up to 25 mcg/L aluminum which may be toxic, particularly for premature neonates due to immature renal function. Parenteral administration of aluminum greater than 4 to 5 mcg/kg/day is associated with central nervous system and bone toxicity *[see Warnings and Precautions (5.5)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Intravenous administration of calcium gluconate increases serum ionized calcium level. Calcium gluconate dissociates into ionized calcium in plasma. Ionized calcium and gluconate are (b) (4) constituents of body fluids.

12.3 Pharmacokinetics

Absorption

Calcium Gluconate Injection is 100% bioavailable following intravenous injection.

Metabolism

Calcium itself does not undergo direct metabolism. The release of ionized calcium from intravenous administration of calcium gluconate is direct and does not seem to be affected by the first pass through the liver.

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 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).

Elimination

Studies have shown a relationship between urinary calcium excretion and the intravenous administration of calcium gluconate, with a significant increase in urinary calcium excretion observed after the intravenous administration of calcium gluconate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Calcium Gluconate Injection. Calcium gluconate was not mutagenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* (strains TA-1535, TA-1537, and TA-1538) or *Saccharomyces cerevisiae* (Strain D4). Fertility studies in animals have not been conducted with calcium gluconate administered by the intravenous route.

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/s/

ARULASANAM K THILAGAR
09/28/2018

CALVIN L ELMORE
09/28/2018
I concur with the recommendation for AP. Same concentration of active pharmaceutical ingredient as in the relied upon listed drug (as administered).