

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208418Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 208418	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: none submitted Established/Proper Name: Calcium Gluconate Injection, USP 10% Dosage Form: Injection Strengths: USP 10%		
Applicant: Fresenius Kabi USA, LLC		
Date of Receipt: May 16, 2016		
PDUFA Goal Date: March 16, 2017		Action Goal Date (if different):
RPM: Meghna M. Jairath, Pharm.D.		
Proposed Indication(s): (b) (4)		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If “YES” contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
published literature	Nonclinical toxicology; clinical Entire application is based on published literature
No listed drug	

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The Applicant is relying on literature for clinical and non clinical, including several randomized, placebo and active controlled clinical trials in different patient populations (neonatal, pediatric, and adult), that evaluate the effect of calcium gluconate on serum calcium and symptoms of hypocalcemia. The submitted literature is scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient contained in the Applicant's drug product. The doses used in the literature support the proposed dose range

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES ☐ NO ☐

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If “**NO**” to (a) proceed to question #11.

If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

*If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If “**NO**”, proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

*If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

MEGHNA M JAIRATH
06/15/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: June 1, 2017

To: Meghna Jairath, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Meena Ramachandra, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208418
OPDP labeling comments for CALCIUM GLUCONATE injection, for intravenous use

On June 20, 2016 OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) and carton/container labeling for CALCIUM GLUCONATE injection, for intravenous use (Calcium Gluconate).

OPDP's review of the proposed substantially complete version of the PI is based on the version e-mailed by Meghna Jairath on May 23, 2017 titled "FK-Comments Calcium Gluconate track changes-SDV.doc" and the carton/container labeling accessed via DARRTS that was submitted by the sponsor on December 9, 2016.

OPDP's comments on the proposed PI are reflected in the attached version of the substantially complete labeling. OPDP has no comments on the proposed carton and container labeling at this time.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Meena Ramachandra at 240-402-1348 or Meena.Ramachandra@fda.hhs.gov.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MEENA RAMACHANDRA
06/01/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone (301) 796-2200
FAX (301) 796-9744

MEMORANDUM

From: Mona Khurana, M.D., Acting Team Leader
Division of Pediatric and Maternal Health (DPMH)
Office of New Drugs (OND)

Erica Radden, M.D. Medical Officer
DPMH, OND

Through: John J. Alexander, M.D., M.P.H., Deputy Division Director
DPMH, OND

To: Division of Metabolism and Endocrinology Products
(DMEP)

Drug: Calcium Gluconate Injection

Application Number: NDA 208418 (IND 113171)

Sponsor: Fresenius Kabi USA

Proposed Indication: (b) (4)

Subject: Review of Pediatric Use Information in Labeling

Consult Request: DMEP consulted the DPMH Pediatrics team on June 20, 2016 to provide recommendations for pediatric use information in labeling.

Materials Reviewed

- DPMH Consult request (dated June 20, 2016)
- Relevant documents under IND 113171 in DARRTS
- Relevant documents under NDA 208418 in DARRTS

- Applicant's proposed labeling (submitted May 16, 2016)

Background

Regulatory History of this Application

On May 16, 2016, the applicant submitted a New Drug Application (NDA) for Calcium Gluconate Injection, United States Pharmacopeia (USP) 10% for the (b) (4) under Section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. The applicant has not conducted any clinical studies and is relying entirely on the literature to support this NDA submission.

The applicant is currently marketing this product as an unapproved drug in the United States and contends that intravenous (IV) calcium gluconate has been commonly used for the correction of hypocalcemia-related symptoms despite the availability of other therapies for the treatment of symptomatic hypocalcemia.¹

Because no calcium gluconate drug products are currently FDA approved, this NDA submission for Calcium Gluconate Injection triggers the requirement for a full pediatric assessment under the Pediatric Research Equity Act (PREA) because the product represents a new active ingredient. Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred or inapplicable.

DMEP issued an Agreed Initial Pediatric Study Plan (iPSP) to the applicant on April 13, 2016. The Agreed iPSP, which was included with this NDA submission, proposes a full pediatric assessment with no requests for partial waiver or deferral of studies in any pediatric age group.

During the filing review of NDA 208418, DMEP noted that the submitted safety database appeared to be acceptable for the adult and neonatal (less than one month of age) populations but that data submitted to support pediatric use outside of the neonatal age range did not appear to be sufficient. DMEP conveyed this potential clinical review issue to the applicant along with recommendations for specific public databases the applicant was advised to search to provide supportive data for product use across the entire pediatric age range.²

¹ Module 2.2 Introduction of NDA 208418

² July 29, 2016 Filing communication to Applicant under NDA 208418:
<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af803f8d8d>; accessed in DARrrTS on May 9, 2017.

The applicant submitted supportive pediatric data as requested by DMEP on February 10, 2017. DMEP considered the applicant's submission to be a major amendment to the NDA and, therefore, extended the goal date for the NDA by three months from March 16, 2017 to June 16, 2017 to provide time for a full review of the submission.³

The DMEP clinical team is recommending product approval in both adults and pediatric patients down to birth based on their review of the published data included in the NDA submission and in the major amendment.

DPMH Review of Pediatric Use Information in Calcium Gluconate Injection Labeling

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. When data support the use of a drug in a pediatric population for a particular indication, pediatric use information must be placed in relevant sections of labeling, as applicable (21 CFR 201.57(c)(9)(iv)(B)(C) and (D)).⁴

This DPMH-Pediatric team labeling review will specifically focus on edits to Sections 1 (Indications and Usage), 2 (Dosage and Administration), 3 (Dosage Forms and Strengths), 4 (Contraindications), 5 (Warnings and Precautions) and 8.4 (Pediatric Use). Excerpts from these sections contain the applicant's proposed labeling superimposed with revisions discussed by DPMH and DMEP at labeling meetings held on May 1st and May 8th. Proposed additions are presented as underlined text and proposed deletions as strikethroughs in the relevant text. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

1 Indications and Usage

Calcium Gluconate Injection is indicated for pediatric and adult patients for the treatment of acute, symptomatic hypocalcemia (b) (4)

³ February 23, 2017 Review Extension Letter to the Applicant under NDA 208418: <http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80428d2c>; accessed in DARRTS on May 9, 2017.

⁴ February 2013 Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm341394.pdf>; accessed May 9, 2017.

(b) (4)

Limitations of Use:

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

DPMH Comments: The term, “pediatric patients,” should be incorporated into the indication statement to clarify this product is being recommended for approval in not only adults but also the full pediatric age range. DPMH agrees with the following DMEP comments discussed during labeling meetings held on May 1st and 8th:

- *The indication statement should clarify that the product will be approved for treatment of acute (b) (4) hypocalcemia.*
- *The term (b) (4) should be deleted from the indication statement (b) (4)*
- *(b) (4)*
- *DMEP’s proposal to add a limitation of use to product labeling (b) (4)*

2 Dosage and Administration

2.1 Important Dosage and Administration Instruction

- Verify the patency of the intravenous line prior to Calcium Gluconate Injection administration to avoid iatrogenic calcinosis cutis [see Warnings and Precautions (5.3)].

(b) (4)

(b) (4)

(b) (4)

DPMH Comments: DMEP proposed the revisions outlined in this subsection. DPMH suggests minor edits to the language in the first bullet to emphasize the importance of ensuring the patency of the IV line prior to Calcium Gluconate Injection administration to avoid iatrogenic calcinosis cutis which may occur with or without extravasation of the calcium solution. DPMH also suggests adding the term, “including neonates,” to the fourth bullet because the pediatric dosing recommendations were derived from data provided in neonates.

2.2 Recommended Dosage

(b) (4)

Table 1 provides dosing recommendations for Calcium Gluconate Injection in mg of calcium gluconate for neonates, pediatric, and adult patients.

(b) (4)

(b) (4)

Table 1. Dosing Recommendations in mg of Calcium Gluconate for Neonate, Pediatric, and Adult Patients

Patient Population	Initial Dose	Subsequent Doses (if needed)
(b) (4)		

DPMH Comments: DMEP proposed the revisions to this section, including addition of a table summarizing the neonatal, pediatric, and adult dosing recommendations. DPMH agrees with the tabular presentation but suggests DMEP consider rounding the dosing recommendations to the nearest 5 mg (e.g. round 29 mg to 30 mg; round (b) (4) mg to (b) (4) mg) to simplify dosing calculations for prescribers.

3 DOSAGE FORMS AND STRENGTHS

Calcium Gluconate Injection, (b) (4) is a clear, colorless to slightly yellow (b) (4) in the following (b) (4)

(b) (4)

Each mL of Calcium Gluconate Injection, (b) (4) contains 9.3 mg (b) (4) 0.465 mEq elemental calcium. (b) (4)

(b) (4)

DPMH Comments: DMEP proposed the revisions to this section. DPMH agrees that the elemental calcium content of the product should be expressed in both milligrams (mg) and milliequivalents (mEq) per one milliliter (mL) (b) (4) to avoid confusion given that single-dose vials will be available in three different volumes (10 mL, 50 mL, and 100 mL). DPMH also agrees with DMEP that the elemental content per mL of this product should also be added to Section 2 adjacent to the table containing adult and pediatric dosing recommendations so prescribers who calculate the calcium deficit for any given patient on the basis of mEq or mg of elemental calcium will be able to determine how much of this product is needed to provide the calculated amount of elemental calcium.

4 CONTRAINDICATIONS

Calcium Gluconate Injection is contraindicated in (b) (4)

(b) (4)

- (b) (4) Hypercalcemia.
- (b) (4) eonates (28 days of age or younger)- receiving ceftriaxone [see Warnings and Precautions (5.2)].

DPMH Comments: In September 2007, FDA issued a Drug Safety Communication (DSC) to healthcare professionals alerting them to important revisions to the Contraindications, Warnings, and Dosage and Administration sections of ceftriaxone labeling.⁵ The new safety information was based on reports of fatal cases in neonates who had received simultaneous administration of ceftriaxone and calcium-containing products. The DSC noted that administration of the two products at different times and via different infusion lines has also been fatal. Since the 2007 DSC, no reported cases of ceftriaxone-calcium precipitates had been reported outside of the neonatal setting, but FDA has maintained the position publicly that the potential for this interaction exists in patients of any age.

In 2009, FDA issued an update to the 2007 DSC describing results from two in vitro studies designed and conducted by Roche, the manufacturer of Rocephin (ceftriaxone) to assess the potential for precipitation of ceftriaxone-calcium precipitates when both products are mixed in vials and in infusion lines.⁶ The studies were conducted in

⁵

<https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm134328.htm>; accessed May 10, 2017.

⁶<https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm084263.htm>; accessed May 10, 2017.

neonatal and adult plasma and looked for ceftriaxone-calcium precipitates using varying concentrations of both drugs including at concentrations exceeding those achieved in vivo. Based on the results, FDA recommended ceftriaxone labeling include a contraindication for use in neonates 28 days of age or younger. FDA stated patients older than 28 days of age could receive ceftriaxone and calcium-containing products sequentially provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.^{7,8}

DPMH discussed the 2007 and 2009 DSCs with DMEP at the May 8th labeling meeting. The contraindication of use for Calcium Gluconate Injection in neonates 28 days of age or younger is consistent with FDA's labeling recommendations conveyed in the 2009 DSC. DPMH suggests cross-referencing to more detailed information in the relevant subsection in Warnings and Precautions as to why product use is contraindicated in neonates receiving ceftriaxone.

5.2 (b) (4) **-End-Organ Damage due to Intravascular Ceftriaxone-Calcium Precipitates**

Concomitant use of ceftriaxone and Calcium Gluconate Injection is contraindicated in neonates 28 days of age or younger due to cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy. (b) (4) precipitates (b) (4) may act as emboli, resulting in vascular spasm or infarction.

[see Contraindications (4)]. 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. Do not administer ceftriaxone simultaneously with Calcium Gluconate Injection via a Y-site in any age group.

(b) (4)

⁷ Bradley JS, Wassel RT, Lee L, et al. Intravenous Ceftriaxone and Calcium in the Neonate: Assessing the Risk for Cardiopulmonary Adverse Events. Pediatrics 123: e609-e613, 2009.

⁸ Steadman E, Raisch DW, Bennett CL, et al. Evaluation of a Potential Clinical Interaction between Ceftriaxone and Calcium. Antimicrobial Agents and Chemotherapy 54(4): 1534-1540, 2010.

5.3 (b) (4) Calcinosis (b) (4)

Intravenous administration of Calcium Gluconate Injection and local trauma may result in calcinosis cutis due to transient increase in local calcium concentration. This condition can occur with or without extravasation of Calcium Gluconate Injection, is characterized by abnormal dermal deposits of calcium salts, and clinically manifests as papules, plaques, or nodules that may be associated with erythema, swelling, or induration. Tissue necrosis, ulceration, and secondary infection are the most serious complications.

If extravasation occurs or clinical manifestations of calcinosis cutis are noted, immediately discontinue intravenous administration at that site and treat as needed.

(b) (4)

DPMH Comments: Iatrogenic calcinosis cutis is well-described in the literature. Two published reports retrieved by this reviewer describe this adverse reaction in an 11 year old girl⁹ and a 9 year old girl,¹⁰ but the rest of the retrieved publications described the occurrence only in neonates and infants less than 2 months of age.^{11,12,13,14,15,16,17,18} All

⁹ Moss J, Syrenglass A, Antaya R, et al. Calcinosis Cutis: A Complication of Intravenous Administration of Calcium Gluconate. Journal of Cutaneous Pathology 33(Supplement 2): 60-62, 2006.

¹⁰ Hsu CH, Chen WY, Tsai TH. A 9-Year-Old Girl with Rhabdomyolysis Complicated with Iatrogenic Calcinosis Cutis. Clinical and Experimental Dermatology 34: e503-e504, 2009.

¹¹ Caksen H and Odabas D. An Infant with Gigantic Subcutaneous Calcium Deposition Following Extravasation of Calcium Gluconate. Pediatric Dermatology 19(3): 277-279, 2002.

¹² Arora A, Agarwal A, Kumar S, et al. Iatrogenic Calcinosis Cutis – a Rare Differential Diagnosis of Soft-Tissue Infection in a Neonate: A Case Report. Journal of Orthopaedic Surgery 13(2): 195-198, 2005.

¹³ Agarwal A and Arora A. Iatrogenic Calcinosis Cutis Following Extravasation of Calcium Gluconate. Journal of Orthopedic Science 13: 576-577, 2008.

retrieved publications implicated calcium gluconate infusion. Two publications note that calcinosis cutis can occur even in the absence of extravasation of the calcium solution.^{10,13}

5.6 Aluminum Toxicity

(b) (4) Calcium Gluconate Injection contains aluminum, up to 400 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.

DPMH Comments: This language is consistent with the January 26, 2000 Final Rule on Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition (65 FR 4103 at 4105). Based on the aluminum content of this product, if the maximum recommended daily dose of Calcium Gluconate Injection of 500 mg/kg/day is administered to a low birth weight preterm neonate weighing 2.5 kg, the neonate would receive 5 mcg/kg of aluminum per day.

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 (2.3)].

Concomitant use of ceftriaxone and Calcium Gluconate Injection is contraindicated (b) (4) 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

¹⁴ Sonohata M, Akiyama T, Fujita I, et al. Neonate with Calcinosis Cutis Following Extravasation of Calcium Gluconate. *Journal of Orthopedic Science* 13: 269-272, 2008.

¹⁵ Chen TK, Yang CY, Chen SJ. Calcinosis Cutis Complicated by Compartment Syndrome following Extravasation of Calcium Gluconate in a Neonate: A Case Report. *Pediatric Neonatology* 51(4): 238-241, 2010.

¹⁶ Ergin H, Karaca A, Ergin S, et al. Calcinosis Cutis in a Newborn with Transient Pseudohypoparathyroidism. *Indian Journal of Pediatrics* 78(11): 1424-1426, 2011.

¹⁷ Vijayalakshmi AM and Devaprasath S. Calcinosis Cutis. *Indian Pediatrics* 48: 582-583, 2011.

¹⁸ Ching D. Iatrogenic Calcinosis Cutis following a Neonatal Extravasation Injury 75(5): 295, 2014.

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 formation of ceftriaxone-calcium precipitates [see Contraindications (4) and Warnings and Precautions (5.2)]. This product contains up to 400 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 (5.6)].

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/s/

MONA K KHURANA
05/12/2017

JOHN J ALEXANDER
05/14/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Office of New Drugs
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Division of Pediatric and Maternal Health Memorandum

Date: May 8, 2017 **Date Consulted:** June 20, 2016

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Meghna M. Jairath, Pharm.D., Regulatory Project Manager (RPM)
Division of Metabolism & Endocrinology Products (DMEP)

Drug: Calcium Gluconate Injection, 10% for intravenous (IV) administration.

NDA: NDA 208418

Applicant: Fresenius Kabi USA, LLC

Subject: Pregnancy and Lactation labeling

Indication: Calcium Gluconate Injection is a super saturated solution of calcium gluconate indicated for (b) (4)

Materials Reviewed:

- Applicant's submitted background package for NDA 208418, submitted as SD#1 on May 16, 2016.
- Applicant's revised label, literature review and summary of pharmacovigilance database submitted as SD#6 on February 10, 2017.
- DPMH review of Calcium Gluconate Injection, 10% for intravenous (IV) administration. IND 113171. January 26, 2016. Erica Radden, M.D., DARRTS Reference ID 3877655.

Consult Question: "Please review labeling for PLLR compliance and provide comments regarding the adequacy of their proposal."

INTRODUCTION

On June 20, 2016, DMEP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of Calcium Gluconate injection, USP 10% labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- May 16, 2016, Fresenius Kabi USA, LLC. submitted a 505(b)(2) New Drug Application (NDA) 208418 for Calcium Gluconate Injection, USP 10%
- Application is relying on published literature
- Currently Calcium Gluconate Injection, USP 10% is a marketed/unapproved product
- Information Request (IR) sent on December 12, 2016 regarding use in pregnant and lactating women with a literature review, summary of pharmacovigilance database and a revised label
- Response to IR received on February 10, 2017

BACKGROUND

Calcium Gluconate Injection, USP 10% and Drug Characteristics¹

- Calcium Gluconate Injection, USP 10% is a sterile, non-pyrogenic, supersaturated solution of calcium gluconate for intravenous use only.
- Each mL contains 94 mg of calcium gluconate, 4.5 mg of calcium saccharate tetrahydrate, hydrochloric acid and/or sodium hydroxide for pH adjustment (6.0 to 8.2) and water for injection, q.s.
- (b) (4) Each 10 mL of Calcium Gluconate Injection, USP 10% provides 93 mg elemental calcium equivalent to (b) (4) calcium gluconate (0.465 elemental calcium [Ca⁺⁺] mEq/mL).
- Molecular weight: 448.39
- The main pharmacodynamic effect is to relieve symptoms associated with hypocalcemia due to changes in the ionized component of serum.
- 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).
- Approximately 80% of orally administered calcium is excreted in the feces as insoluble salts; urinary excretion accounts for the remaining 20%.

¹ Calcium Gluconate Injection 10% proposed labeling

- The intravenous infusion of calcium can increase blood pressure. However, rapid intravenous injection of calcium salts may cause vasodilatation, decreased blood pressure, bradycardia, cardiac arrhythmias and cardiac arrest.

Normal Calcium Physiology during Pregnancy and Lactation²

Pregnancy and lactation are associated with profound changes in calcium physiology. The need for mineralization of the fetal skeleton [which requires around 30 g of calcium during the whole of pregnancy (the majority in the third trimester (TM))] creates a large demand on the mother for calcium. In most situations an increase in maternal calcium absorption provides the additional calcium which increases from approximately 200 mg per day (non-pregnant state) to approximately 400 mg per day in the third trimester. This increase appears to be mediated by an increase in maternal 1, 25- dihydroxyvitamin D [the most active form of vitamin D (calcitriol)]. The increase in calcitriol occurs despite parathyroid hormone (PTH) levels (the normal stimulus for the production of active vitamin D within the kidney) decreasing during early pregnancy before slowly returning to the normal range. The increased production of active vitamin D is likely due to production from the placenta or through production of parathyroid hormone-related protein (PTHrP) by the placenta. PTHrP is made by a range of fetal tissues and in addition, by maternal breast tissue.

An important thing to recognize regarding calcium physiology during pregnancy is that the serum albumin concentration falls during the first TM of pregnancy due to hemodilution. Since approximately 50% of total calcium is normally bound to albumin this leads to a corresponding decrease in total calcium. However, albumin corrected calcium and ionized calcium (the clinically relevant form) should be unchanged throughout pregnancy. Bone turnover (the amount of bone resorbed and formed throughout the whole skeleton) appears to increase in early pregnancy and remains high throughout.^{3,4}

The changes in calcium balance during lactation are very different from those seen during pregnancy. Approximately 300–1000 mg of calcium is lost in breast milk per day. In contrast to pregnancy this supply of additional calcium is not provided through an increase in gastrointestinal absorption but rather through an increase in net maternal bone resorption and release of calcium from bone into the systemic circulation. There is a decrease in estrogen and the level of active vitamin D returns to normal. The level of PTH decreases and the level of PTHrP increases as a consequence of production from breast tissue. Between 3-10% of bone mass is lost during lactation but this recovers very quickly upon weaning.

Hypocalcemia and Pregnancy

Hypoparathyroidism and vitamin D deficiency have been reported as etiologies for hypocalcemia during pregnancy. A single case report of three pregnancies in 2 women with

² Cooper MS. Disorders of calcium metabolism and parathyroid disease. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2011; 25: 975-983.

³ Naylor KE *et al.* The effect of pregnancy on bone density and bone turnover. *Journal of Bone Mineral Research* 2000; 15: 129–137.

⁴ Black AJ *et al.* A detailed assessment of alterations in bone turnover, calcium homeostasis, and bone density in normal pregnancy. *Journal of Bone Mineral Research* 2000; 15: 557–563.

autosomal dominant hypocalcemic hypercalciuric nephrocalcinosis was also identified in the published literature. Hypoparathyroidism refers to the failure of the body to produce levels of PTH sufficient to maintain a normal level of serum calcium. Most commonly it is secondary to thyroid or parathyroid surgery and removal of parathyroid tissue. It can also develop spontaneously through failure to develop parathyroid tissue or through autoimmune parathyroid tissue destruction. Gradual development of hypocalcemia may be minimally symptomatic, resulting in muscle twitches, associated with perioral and peripheral paresthesias. Rapidly developing hypocalcemia can be life-threatening and can progress to tetany and seizures. Treatment involves the use of active Vitamin D analogues and calcium. The absence of PTH prevents conversion of 25-hydroxyvitamin D to calcitriol so “active vitamin D” analogues are required. Patients stabilized on active Vitamin D analogues pre-pregnancy are likely to need some adjustment during pregnancy.^{5,6} A critical part of this strategy is the expectation that the requirement for active Vitamin D treatment will change dramatically post-parturition. Failure to recognize this could result in life threatening hypo- or hypercalcemia.⁷

Historically, vitamin D deficiency when severe presented as rickets with soft bones and abnormal development of the pelvis leading to complications with vaginal delivery. Modern day Vitamin D deficiency rarely presents in this fashion but concern about more subtle adverse effects on both mother and infant persist. Low vitamin D levels may, for example, be a risk factor for eclampsia. Women with a high intake of vitamin D had a reduced risk of preeclampsia in one study⁸ but not all studies have shown such associations.⁹ Low vitamin D levels have also been associated with increased insulin resistance during pregnancy¹⁰ and an increased rate of caesarian section.¹¹

It is much clearer that maternal vitamin D deficiency can be a risk to the neonate. Most commonly, substantial maternal vitamin D deficiency becomes apparent when an exclusively breast fed infant develops seizures associated with hypocalcemia.¹² Cardiomyopathy can also occur in this setting, which resolves with replacement of calcium and vitamin D.¹³ There is emerging evidence from multiple sources that maternal vitamin D levels have a significant impact on bone development in utero and during childhood. Maternal vitamin D

⁵ Callies F *et al.* Management of hypoparathyroidism during pregnancy – Report of twelve cases. *European Journal of Endocrinology.* 1998; 139: 284–289.

⁶ Salle BL *et al.* Hypoparathyroidism during pregnancy: treatment with calcitriol. *Journal of Clinical Endocrinology & Metabolism* 1981; 52: 810–813.

⁷ Caplan RH & Beguin EA. Hypercalcemia in a calcitriol-treated hypoparathyroid woman during lactation. *Obstetrics & Gynecology* 1990; 76: 485–489.

⁸ Haugen M *et al.* Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. *Epidemiology* 2009; 20: 720–726.

⁹ Shand AW *et al.* Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for pre-eclampsia. *British Journal of Obstetrics and Gynecology* 2010; 117: 1593–1598.

¹⁰ Maghbooli Z *et al.* Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. *Diabetes/Metabolism Research and Reviews* 2008; 24: 27–32.

¹¹ Merewood A *et al.* Association between vitamin D deficiency and primary cesarean section. *Journal of Clinical Endocrinology & Metabolism* 2009; 94: 940–945.

¹² Robinson PD *et al.* The re-emerging burden of rickets: a decade of experience from Sydney. *Archives of Disease in Childhood* 2006; 91: 564–568.

¹³ Maiya S *et al.* Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. *Heart* 2008; 94: 581–584.

deficiency was linked with reduced bone mineral content in childhood (at age 9).¹⁴ Using high-resolution ultrasound the same group demonstrated that vitamin D deficiency (defined as 25-hydroxyvitamin D levels of less than 25 nmol/L) is linked with splaying of the femoral metaphysis in utero, a feature commonly seen in infantile rickets.¹⁵ These data indicate that the changes seen in childhood have their origins in utero. Supporting a role for vitamin D levels considered to be in the normal range during bone development in utero, another group examined bone content and area of the tibia using quantitative CT.¹⁶ They found that women with 25-hydroxyvitamin D levels above a mean level of 42 nmol/L gave birth to neonates with greater bone mineral content and greater cross-sectional areas than women with levels below 42 nmol/L. The recommended vitamin D allowance in pregnancy is 600 IU per day according to recent Institute of Medicine guidelines.¹⁷ The upper recommended level of intake is 4000 IU per day.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹⁸ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹⁹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical Experience

According to the pharmacology/toxicology team leader (email communication dated 3/23/17)

The Applicant conducted no nonclinical studies themselves. They provided references to published nonclinical studies with calcium and/or gluconate, but

¹⁴ Javaid MK *et al.* Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet* 2006; 367: 36–43.

¹⁵ Mahon P *et al.* Low maternal vitamin D status and fetal bone development: cohort study. *Journal of Bone Mineral Research* 2010; 25: 14–19.

¹⁶ Viljakainen HT *et al.* Maternal vitamin D status determines bone variables in the newborn. *Journal of Clinical Endocrinology & Metabolism* 2010; 95: 1749–1757.

¹⁷ Ross AC *et al.* The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *Journal of Clinical Endocrinology & Metabolism* 2011; 96: 53–58.

¹⁸ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹⁹ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

these reports are mostly of suspect quality and are of limited relevance to this product given the indication... we have very low concern for the safety of the gluconate portion of the product (it is also found endogenously and is present in other drugs), we have limited concern for reproductive toxicity with the drug product itself in the acute setting... That said, calcium is mined from the earth and gluconate is a metal “chelator” (binder). In fact, this product contains unacceptable levels of (b) (4) aluminum that are too high to support (b) (4), repeat-dose administration in anyone, much less in pregnant patients... So, if this product is to be used as indicated (and this product will continue to be used whether it is approved or not), Pharm/Tox will likely recommend approval with very limited or no animal data in labeling. We will recommend this product only be used for a single-dose or very short duration to treat symptomatic hypocalcemia, since over time the (non-calcium) metal content (e.g., (b) (4) aluminum) would lead to unacceptable exposures.

For further details, the reader is directed to the Nonclinical Review by Arulasanam Thilagar, PhD.

Applicant’s Review of Literature

Fresenius Kabi performed a literature search in EMBASE (search date January 3, 2017) using the following broad search string and filters: For "calcium gluconate" and "lactation" and found 8 articles. According to the applicant, none of the publications mentioned "calcium gluconate" in the abstract, but the search details showed it was in the text of the article. None of the publications were considered by the applicant to be “adequate to assess the safety of calcium gluconate with regard to the new FDA pregnancy subsections Pregnancy (includes labor and delivery), Lactation (includes nursing mothers), and Females and males of reproductive potential”. Two of the eight articles (those authored by Krysiak and Shah) are considered relevant and have been described below in Table 1 under “DPMH’s Review of Literature”.

DPMH’s Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms “calcium gluconate injection and pregnancy,” “calcium gluconate injection and pregnant women,” “calcium gluconate injection and pregnancy and birth defects,” “calcium gluconate injection and pregnancy and congenital malformations,” “calcium gluconate injection and pregnancy and stillbirth,” “calcium gluconate injection and spontaneous abortion” and “calcium gluconate injection and pregnancy and miscarriage.” No reports of adequate and well-controlled studies of calcium gluconate injection use in pregnant women were found. The case reports identified are described below in Table 1:

Table 1: Pregnancies in Women with Hypocalcemia Exposed to Calcium Gluconate Injection

Case Report #/ Author/ Year	Maternal Age (yrs.)	Disease type/Age at Diagnosis	Estimated Fetal Exposure	Pregnancy outcome/EGA*	Perinatal Conditions	Concomitant meds/ Confounders
#1 Aceto ²⁰ 1966	21	Congenital Hypoparathyroidism (HypoPTH)/ 16	At time of birth given to relieve carpopedal spasms	Vaginal delivery of a 3 lb 9 oz. female at 34 weeks (wks), mother unresponsive with seizures post delivery	Infant with cyanosis and flaccidity, required intubation, Bony changes c/w possible infantile hyperparathyroidism-clavicles, humeri, bones of the forearm and lower extremities had decreased modeling of the shaft of the bones, Infant with developmental delays noted at 11, 15 and 21 months	Vitamin (vit) D and oral calcium (Ca)/ Maternal gestational hypertension, pyelonephritis, renal calculi
#2 Bakas ²¹ 2014	36	HypoPTH/ 26	At time of birth	Elective Cesarean section (C-section) at 39 wks	Healthy female 3380 grams (gm)	Calcitriol, Ca, L-thyroxine
#3 Krysiak ²² 2011	32	HypoPTH 2° to thyroid surgery/ 29	Wk 20	Premature labor at 20 wks , Delivered (?vaginally) at 38 wks	Healthy infant 3650 gm	Verapamil, phenoterol, magnesium sulfate at 20 wks
#4 Shah ²³	38	HypoPTH 2° to thyroid surgery/ 34	Wk 37	“Normal” delivery at ? 37 wks	Healthy infant 2800 gm	Calcitriol, Ca, L-thyroxine

*EGA=estimated gestational age

Source: Reviewer’s table

²⁰ Aceto T *et al.* Intrauterine Hyperparathyroidism: A Complication of Untreated Maternal Hypoparathyroidism. J Clin Endocr. 1966. 26: 487-492.

²¹ Bakas P *et al.* Secondary Hypoparathyroidism during Pregnancy- A Case Report and Review of the Literature. Clinical and Experimental Obstetrics and Gynecology. 2015; XLII (6): 825-826.

²² Krysiak R *et al.* Hypoparathyroidism in pregnancy. Gynecological Endocrinology, August 2011; 27(8): 529–532.

²³ Shah KH *et al.* BMJ Case Rep 2015. doi:10.1136/bcr-2015-210228.

In Micromedex²⁴, the authors cite the product information for calcium acetate oral capsules²⁵ and note “Fetal harm is not expected if the maternal calcium levels are maintained within the normal range. Hypercalcemia during pregnancy may increase the risk for maternal and neonatal complications, such as stillbirth, preterm delivery, and neonatal hypocalcemia and hypoparathyroidism”.

Multiple case reports were noted during the literature review that involved pregnant women with hypocalcemia, some treated with other formulations of calcium. Since these are likely relevant with regard to potential fetal and maternal outcomes, I have included these in an additional table below.

²⁴ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 3/15/16.

²⁵ Product Information: calcium acetate oral capsules, calcium acetate oral capsules. Roxane Laboratories, Inc. (per DailyMed), Columbus, OH, 2012.

Table 2: Pregnancies in Women with Hypocalcemia +/- Treatment with Calcium

Case Report #/ Author/ Year	Maternal Age (yrs.)	Disease type/Age at Diagnosis	Estimated Fetal Exposure	Pregnancy outcome/EGA*	Perinatal Conditions
#1 Bronsky ²⁶ 1968	Patient A= 19 years at 4 th pregnancy,	Hypoparathyroidism (HypoPTH)/ 19	20 th week presented with a Ca=5.5 in tetany, treated with Vitamin D, calcium lactate and aluminum hydroxide gel	Spontaneous abortion (SAB) at 26 weeks	
#2	Patient A= 20 years at 5 th pregnancy	same	Took Vitamin D, calcium lactate and aluminum hydroxide gel up to 5 th month	Term delivery	2320 gm male infant with marked demineralization of ribs, clavicle + scapulae, bowing and subperiosteal resorption of the long bones
#3	Patient B= Age not reported	HypoPTH 2° to thyroid surgery	Took dihydrotachysterol, calcium lactate and aluminum hydroxide gel up to 6th month	Term delivery	2200 gm female infant with no bony abnormalities, VSD with pulmonary stenosis diagnosed at one year
#4 Camadoo ²⁷ 2007	Age not reported	Hypocalcemic 2° to vitamin D deficiency	No supplementation during pregnancy	Not reported	Generalized seizures at one week of age 2° to Ca= 6.3mg/dl

²⁶ Bronsky D *et al.* Intra-uterine Hyperparathyroidism Secondary to Maternal Hypoparathyroidism. *Pediatrics*. 1968; 42 (4):606-613.

²⁷ Camadoo L *et al.* Case Report: Maternal vitamin D deficiency associated with neonatal hypocalcemic convulsions. *Nutrition Journal*. 2007;6: 23:1-2.

Case Report #/ Author/ Year	Maternal Age (yrs.)	Disease type/Age at Diagnosis	Estimated Fetal Exposure	Pregnancy outcome/EGA*	Perinatal Conditions
#5 Eastell ²⁸ 1985	23 at 1 st pregnancy	Not diagnosed		Premature labor at 27 weeks	790 gm female died at day 2
#6	24 at 2 nd pregnancy	Hypocalcemia diagnosed at age 24		Premature labor at 18 weeks	No details provided on infant
#7	25 at 3 rd pregnancy	HypoPTH	Treated with alfacalcidol	Delivery at 36 weeks	Normal infant
#8 Ruffini ²⁹ 2015	Not reported	Hypocalcemic 2° to vitamin D deficiency	none	Term delivery	4080 gm female infant with spasms of muscles on day 6 of life due to Ca=5.7 mg/dl, found to be vit D deficient
#9 Salle ³⁰ 1981	30	Idiopathic HypoPTH	Calcitriol, vit D, oral Ca	Twins delivered via C-section at 37 wks	Twin A=2300 gm male with ↑ Mineralization of skull and long bones, Twin B=1900 gm female with seizures and hypotonia

*ADHHN= Autosomal Dominant Hypocalcemic Hypercalciuric Nephrocalcinosis

Source: Reviewer's Table

²⁸ Eastell R *et al.* Prolonged hypoparathyroidism presenting eventually as second trimester abortion. BMJ. 1985; 291: 955-956.

²⁹ Ruffini E *et al.* Maternal Vitamin D Deficiency as a Cause of Hypocalcemic Convulsion in a Newborn from Foreign Parents: A Re-emerging Public Health Issue in Western Countries? Minerva Pediatrica.2015; 67(5): 451-452.

³⁰ Salle BL *et al.* Hypoparathyroidism during Pregnancy: Treatment with Calcitriol. Journal of Clinical Endocrinology and Metabolism. 1981; 52(4):810-813.

Pharmacovigilance Database Summary

According to the applicant, since development, there were no cases identified specific to the use during pregnancy and lactation, therefore no relevant cases have been reported.

Summary

There were available data in the published literature with Calcium Gluconate Injection use in pregnant women which were insufficient to inform a drug associated risk of adverse developmental outcomes. There are risks to the mother associated with hypocalcemia in pregnancy including an increased rate of spontaneous abortion, premature and dysfunctional labor, and possibly preeclampsia. 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 (ranging from myotonic jerks to seizures), apnea, cyanosis and cardiac rhythm disorders.

Lactation

Applicant's Review of Literature

See section entitled "Applicant's Review of Literature" under **Pregnancy**. None of the eight articles identified by the applicant were considered relevant to the topic of calcium gluconate injection and lactation.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*³¹, the Drugs and Lactation Database (LactMed),³² Micromedex²⁴, and of published literature in PubMed and Embase using the search terms "calcium gluconate injection and lactation" and "calcium gluconate injection and breastfeeding."

Calcium gluconate injection is not referenced in Hale's *Medications and Mother's Milk*²⁶ or in LactMed.²⁷

In Micromedex,²⁴ the authors note "Infant risk cannot be ruled out" but go on to state

³¹ Hale, Thomas (2012) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing, pg. 422-423.

³² <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Calcium is secreted in breast milk in significant amounts³³. However, infant harm is not expected if the maternal calcium levels are maintained within the normal range. Adverse effects in nursing infants have not been reported. It is not known whether calcium affects the quantity or composition of breast milk.

One article describing a study of oral calcium supplementation in lactating mothers in Gambia was identified in the literature search and is summarized below:

- In a study involving 60 women from the rural villages of Gambia (16 to 41 years of age), measured calcium levels in breast milk did not differ significantly between those receiving calcium supplementation and those receiving placebo. Lactating women were randomly assigned to receive placebo (n=30) or calcium carbonate 1000 mg (n=30) 5 days a week for 12 months. Samples of breast milk, fasting blood, and a 24-hour urine collection were taken at baseline and at 13, 52, and 78 weeks postpartum. Additional samples of breast milk were also collected on weeks 6, 19, 26, 39, and 65. There were no significant differences among the placebo and supplement group during any time of the study from weeks 6 to 78 regarding breast milk calcium concentration adjusted for stage of lactation, age, parity, season, or calcium intake.

The efficacy supplement that is the subject of this review includes neonates in the indication being sought. In the previously referenced DPMH pediatric consult review of the iPSP³⁴ for this submission, dated Jan 2016, the reviewer noted

In neonates (≤ 1 month of age), the sponsor provided literature data to support dosing, safety and efficacy. To support efficacy and safety of the proposed dose, the sponsor referenced three randomized placebo controlled studies and seven case reports of neonates with hypocalcemia treated with calcium. To support safety in neonates, the sponsor referenced three randomized, placebo-controlled trials; five observational studies; one retrospective study; and 17 case reports... Sufficient efficacy data appears to be provided for neonates (including preterm infants)... Although the sponsor's plan to rely solely on literature to support approval of calcium gluconate is potentially acceptable, the data provided appears insufficient to support safety for patients 1 month to 17 years of age and the maximum recommended doses in all pediatric patients because the sponsor has provided no safety data in patients receiving the maximum dose.

Reviewer Comments

It is notable that the one pediatric age group for which sufficient safety information was provided by the applicant was the birth to one month age group (including preterm infants).

³³ Hardman JG, Molinoff PB, & Gilman AG Hardman JG, Molinoff PB, & Gilman AG (Eds): Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th. McGraw-Hill, New York, NY, 1996.

³⁴ DPMH review of Calcium Gluconate Injection, 10% for intravenous (IV) administration. IND 113171. January 26, 2016. Erica Radden, M.D., DARRTS Reference ID 3877655.

Summary

Given the available published information regarding the use of calcium gluconate given directly to neonates, there does not appear to be any reason for concern regarding short term and limited use of calcium gluconate in nursing mothers. DPMH recommends that the following risk/benefit statement be included in section 8.2 of labeling:

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

Use in Females and Males of Reproductive Potential

Nonclinical Experience

No studies have been performed on Calcium Gluconate Injection to assess carcinogenic potential, mutagenesis, or impairment of fertility. However, data are available for the individual components of Calcium Gluconate Injection as summarized below:

Gluconate salts, including calcium gluconate, are not mutagenic in the Ames test; calcium gluconate did not exhibit genotoxicity in the Salmonella typhimurium strains TA-1535, TA-1537, and TA-1538 or Saccharomyces cerevisiae strain D4.

For further details, the reader is directed to the Nonclinical Review by Arulasanam Thilagar, PhD.

Applicant's Review of Literature

See section entitled "Applicant's Review of Literature" under **Pregnancy**. There were no articles identified by the applicant relevant to the topic of calcium gluconate injection and fertility.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding calcium gluconate injection and its effects on fertility and found no relevant literature.

Summary

Since there is no information available on the effect of calcium gluconate injection on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in crisaborole labeling.

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for calcium gluconate injection labeling:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of calcium gluconate injection labeling was structured in the PLLR format to include the “Risk Summary” section.³⁵
- **Lactation, Section 8.2**
 - The “Lactation” subsection of calcium gluconate injection labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” sections.³⁶

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of calcium gluconate injection labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Calcium Gluconate Injection Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 Use in Specific Populations

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. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

³⁵ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

³⁶ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

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 (b) (4), 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 carbonate 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.

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/s/

JANE E LIEDTKA
05/08/2017

LYNNE P YAO
05/11/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 9, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208418
Product Name and Strength:	Calcium gluconate injection, 100 mg/mL
Submission Date:	December 9, 2016
Applicant/Sponsor Name:	Fresenius Kabi
OSE RCM #:	2016-1264-1
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container label and carton labeling for calcium gluconate (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling for calcium gluconate is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Vee, S. Label and Labeling Review for calcium gluconate (NDA 208418). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 NOV 21. 32 p. OSE RCM No.: 2016-1264.

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/s/

SARAH K VEE
01/09/2017

HINA S MEHTA
01/10/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 21, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208418
Product Name and Strength:	Calcium gluconate injection, USP 10%
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	Fresenius Kabi
Submission Date:	May 16, 2016 and August 11, 2016
OSE RCM #:	2016-1264
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed vial label, carton labeling, and Prescribing Information (PI) for calcium gluconate, NDA 208418. The Division of Metabolism and Endocrinology Products (DMEP) requested that DMEPA review the labels and labeling for areas of vulnerability that may lead to medication errors.

Calcium gluconate injection, USP 10% is currently on the market as an unapproved drug and the company submitted the NDA to receive Agency approval.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	B
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. We note that the proposed prescribing information (PI), container and carton labels and labeling contain concentration expressions in (b) (4) mg/mL. The dosage and administration of the product is in mg, thus the (b) (4) designation is not appropriate and should be removed since it may cause calculation errors and confusion.

We note that the labels and labeling contain the term, (b) (4), which is inconsistent with the draft guidance^a. We defer to CMC for the determination of the appropriate package type term on labels and labeling.

^a Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Delete all concentration expression as a (b) (4) from the PI. (b) (4)
(b) (4)
(b) (4) We defer to DMEP and CMC to determine the appropriate concentration of the product.
- B. Highlights, Dosage and Administration
1. Consider moving the dosage ranges for children and adults in separate bullets; as currently displayed the information is difficult to tease out. For example:
(b) (4)
- C. Highlights, Dosage From and Strength
1. Add a bullet stating there are 10 mL, 50 mL, and 100 mL vials.
- D. Full Prescribing Information, Section 2 Dosage and Administration
1. In section 2.2 Recommended Dosage in Adults consider separating out information into bullets for increased readability.
- E. Full Prescribing Information, Section 16, How Supplied/Storage and Handling
1. Add a sentence for the Pharmacy Bulk package (100 mL vial) stating it must be used within 4 hours from initial entry.
- F. We note that the labels and labeling contain the term, (b) (4), which is inconsistent with the draft guidance^b. We defer to CMC for the determination of the appropriate package type term on labels and labeling.

^b Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015.

Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

^c Institute for Safe Medication Practices. It doesn't pay to play the percentages. ISMP Med Saf Alert Acute Care. 2002;7(21):1-2.

^d Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

^e Food and Drug Administration. *Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Error*, April 2016. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

4.2 RECOMMENDATIONS FOR FRESENIUS KABI

We recommend the following be implemented prior to approval of this NDA:

- A. Delete all concentration expression as a (b) (4) from the carton and container labeling. (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Calcium gluconate that Fresenius Kabi submitted on May 13, 2016.

Table 2. Relevant Product Information for Calcium gluconate					
Initial Approval Date	N/A				
Active Ingredient	Calcium gluconate				
Indication	(b) (4)				
Route of Administration	Intravenous injection				
Dosage Form	Injection				
Strength	100 mg/mL				
Dose and Frequency	(b) (4) The dose ranges from 29 mg/kg/dose to (b) (4) mg/kg/dose (b) (4) (children ages 1 month to 17 years) to 1,000 mg/dose to 2,000 mg/dose (b) (4) (adults).				
How Supplied	<table><tr><th>Strength/Vial Size (mL)</th></tr><tr><td>1 gram per 10 mL (100 mg per mL), in a 10 mL plastic vial, packaged in a tray of 25.</td></tr><tr><td>5 grams per 50 mL (100 mg per mL), in a 50 mL plastic vial, packaged in a tray of 25.</td></tr><tr><td>10 grams per 100 mL (100 mg per mL), in a 100 mL plastic vial, packaged in a tray of 20.</td></tr></table>	Strength/Vial Size (mL)	1 gram per 10 mL (100 mg per mL), in a 10 mL plastic vial, packaged in a tray of 25.	5 grams per 50 mL (100 mg per mL), in a 50 mL plastic vial, packaged in a tray of 25.	10 grams per 100 mL (100 mg per mL), in a 100 mL plastic vial, packaged in a tray of 20.
Strength/Vial Size (mL)					
1 gram per 10 mL (100 mg per mL), in a 10 mL plastic vial, packaged in a tray of 25.					
5 grams per 50 mL (100 mg per mL), in a 50 mL plastic vial, packaged in a tray of 25.					
10 grams per 100 mL (100 mg per mL), in a 100 mL plastic vial, packaged in a tray of 20.					
Storage	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not (b) (4) freeze.				
Container Closure	Primary: (b) (4) vials (b) (4)				

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on June 28, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.^f

Table 3: FAERS Search Strategy	
Date Range	January 1, 2010 to June 28, 2016
Product	Calcium gluconate [active ingredient]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

B.2 Results

Our search retrieved 12 cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic

^f The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
11/21/2016

HINA S MEHTA
11/22/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208418 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: none submitted Established/Proper Name: Calcium Gluconate Injection, USP 10% Dosage Form: Injection Strengths: USP 10%		
Applicant: Fresenius Kabi USA, LLC Agent for Applicant (if applicable):		
Date of Application: May 16, 2016 Date of Receipt: May 16, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: March 16, 2017		Action Goal Date (if different):
Filing Date: July 15, 2016		Date of Filing Meeting: July 7, 2016
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☒ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification: The application will be a priority review if: • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): n/a				
List referenced IND Number(s): PIND 113171				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	☒	☐		
Are the established/proper and applicant names correct in electronic archive? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☒		
If yes, explain in comment column.					
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐	x	
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>) ☒ Paid 1/12/16 (PDFUA payment) ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>		☒	☐		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:																					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		☐	☒																		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		☐	☒																		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		☐	☒																		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>																					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		☐	☒																		
If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>						Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																					
Exclusivity	YES	NO	NA	Comment																	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒																			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☒	☐																		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☐	☒	☐																		
If yes, # years requested:																					
Note: An applicant can receive exclusivity without requesting it;																					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	☐	☐	☐	
If yes, contact the Orange Book Staff (CDER-Orange Book Staff).				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	☐	☐	☒	
If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☒ legible	☒	☐		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☒	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <u>paper</u> forms and certifications with hand-written signatures must be included.</i> Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	No relevant patents
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☐	☐	x	No studies done by sponsor
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	All electronic
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	☒	☐		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	☒	☐	☐	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☒	☐	☐	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
BPCA:				
Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☐	☒	☐	Sponsor has no plans to submit one.
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR)	☒	☐		

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

format? ⁴				
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☐	☐	☐	
Has all labeling (PI), carton and immediate container labeling]) been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (send WORD version if available)	☐	☐	☒	
Has all labeling (PI) carton and immediate container labeling, PI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	☐	☒	☐	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	☐	☒		
Any Special Protocol Assessments (SPAs)? Date(s):	☐	x		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 7, 2016

BACKGROUND: This is a 505(b)(2) NDA relying entirely on published literature. The product is calcium gluconate injection which is a marketed, unapproved drug. Applicant is seeking for the (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Meghna M. Jairath	Y
	CPMS/TL:	Pamela Lucarelli	Y
Cross-Discipline Team Leader (CDTL)			
Division Director/Deputy			
Office Director/Deputy			
Clinical	Reviewer:	John Sharretts	Y
	TL:	Marina Zemskova	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Renu Singh	Y
	TL:	Jaya Vaidyanathan	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		

	TL:		
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Nonclinical (Pharmacology/Toxicology)	Reviewer:	Arulasanam Thilagar	Y
	TL:	Calvin (Lee) Elmore	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Suong Tran	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Ankur Kalola	
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sara Vee	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline	Reviewer:		
	TL:		
Other attendees	Sara Stradley, ADRA		Y
	Elizabeth Hanan, Safety RPM		Y
	Denise Pica-Branco, DPMH RPM		Y
	John Alexander, DPMH		Y
	Erica Radden, Peds Clinical Reviewer		Y
	Carol Kasten, Maternal Health Reviewer		Y
	Tamara Johnson, DPMH		Y
	Shannon Sullivan, MD, DMEP		Y
	Deveonne Hamilton-Stokes, OSE, RPM		Y
	Selena Ready, OSE, DPV		Y
	Sally Loewke, OND IO		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: ☐ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ☐ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):		☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO	

If no, explain:	
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain: No clinical studies were conducted.	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined The application did not raise significant safety or efficacy issues.
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jean-Marc Guettier, M.D., Division Director Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): TBD 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

MEGHNA M JAIRATH
07/29/2016

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208418

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Calcium Gluconate Injection, USP 10%

Applicant: Fresenius Kabi USA, LLC

Receipt Date: May 16, 2016

Goal Date: March 16, 2017

1. Regulatory History and Applicant's Main Proposals

This is a 505(b)(2) NDA relying entirely on published literature. The product is calcium gluconate injection which is a marketed, unapproved drug. Applicant is seeking for the (b) (4)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 19, 2016. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *Sponsor requested a waiver in the submission.*

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information

• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

Selected Requirements of Prescribing Information

“**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment: First letter of the following words "in" and "with" should be changed to upper case.
- NO** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: The number "10" is missing preceding "OVERDOSAGE".
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

MEGHNA M JAIRATH
07/28/2016