

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201849Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 201849	NDA Supplement #: S- 000	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: glucagon Dosage Form: sterile lyophilized powder for injection Strengths: 1 mg		
Applicant: Fresenius Kabi USA, LLC		
Date of Receipt: August 8, 2014 – resubmission after CR September 27, 2012		
PDUFA Goal Date: May 8, 2015		Action Goal Date (if different):
RPM: Elisabeth Hanan		
Proposed Indication(s): For use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract		

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)
GlucaGen NDA 020918	FDA's previous findings of safety and efficacy (nonclinical and clinical)

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

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

On September 30, 2010, APP Pharmaceuticals, LCC (APP), submitted a 505(b)(2) New Drug Application (NDA) which relied on FDA's previous finding of safety and effectiveness for the listed drug (LD) GlucaGen NDA 020918. FDA received this application on October 5, 2010.

APP performed a pharmacokinetic (PK) bioequivalence (BE) study of APP's proposed glucagon for injection drug product in comparison to the LD's formulation, via the intramuscular route, in healthy adult subjects. The goal of the study was to demonstrate that the change in manufacturing processes of the glucagon active pharmaceutical ingredient of the proposed drug product versus that of the LD resulted in bioequivalent products. APP's proposed drug product is manufactured by solid phase synthetic process and the LD drug product is manufactured by recombinant process.

Other than the BE study, APP did not perform any duplicative non-clinical, clinical pharmacology, efficacy, or safety studies in support of the 505(b)(2) NDA submitted on September 30, 2010.

On December 3, 2010, FDA issued a Refuse to File (RTF) letter due to non-clinical deficiencies.

APP resubmitted the NDA on November 30, 2011, post-RTF, with no additional BE studies. (b) (4)

(b) (4)
Effective August 1, 2012, APP changed its legal entity name to Fresenius Kabi USA, LLC (Fresenius Kabi).

On September 27, 2012, FDA issued a Complete Response (CR) due to clinical pharmacology and facility inspection deficiencies.

Fresenius Kabi resubmitted the NDA on August 8, 2014. This resubmission included study AA9843, "Bioequivalence of a Test Formulation of Glucagon for SC Injection Compared to Glucagon for Injection (Bedford Laboratories) Under Fasted Conditions," which was conducted to address the clinical pharmacology deficiencies identified in the previous review cycle. The

applicant [REDACTED] ^{(b) (4)} in this resubmission, which was the product manufactured at the facility identified with deficiencies at the previous review cycle. The applicant is only seeking the diagnostic aid indication at this time.

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).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

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)
GlucaGen (glucagon [rDNA origin] for injection)	020918	Y

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: **Novo Nordisk's GlucaGen (NDA 020918) is a recombinant DNA product produced by *Saccharomyces cerevisiae*. GlucaGen was approved in a 505(b)(2) application relying on FDA's previous findings of safety and effectiveness for Eli Lilly's glucagon product (NDA 012122), which (b)(4) is no longer on the market.**

- 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”).

This product provides the same active ingredient, indication, route of administration, and dosage form as the listed drug, GlucaGen. The applicant is not seeking the hypoglycemia indication or the subcutaneous route of administration that are approved under the listed product. This product is a synthetic form of glucagon, whereas the listed drug is a recombinant form of glucagon.

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 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

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)

The applicant provided Paragraph I Certification in their submission dated October 5, 2010.

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/

ELISABETH A HANAN
05/08/2015

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: April 22, 2015
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 201849
Product Name and Strength: Glucagon for Injection, 1 mg/vial
Submission Date: April 16, 2015
Applicant/Sponsor Name: Fresenius Kabi
OSE RCM #: 2015-912
DMEPA Primary Reviewer: Sarah K. Vee, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

DMEP requested that we review the revised container label [REDACTED] (b)(4) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions consist of a new company trade dress, layout, and color changes.

2 CONCLUSIONS

The revised container label [REDACTED] (b)(4) are acceptable from a medication error perspective.

2 Pages 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/

SARAH K VEE
04/23/2015

YELENA L MASLOV
04/23/2015

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

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

Memorandum

Date: April 21, 2015

To: Elisabeth A. Hanan, M.S., Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 201849
OPDP labeling comments for GLUCAGON for Injection, for
intravenous or intramuscular use

On August 20, 2014, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) and carton/containers for GLUCAGON for Injection, for intravenous or intramuscular use. OPDP's comments on the proposed draft PI are based on the version sent by Elisabeth Hanan via email on April 16, 2015 and are marked on the version provided directly below.

OPDP does not have any comments regarding the carton/containers at this time.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

11 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

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/s/

CHARUNI P SHAH
04/22/2015



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins

Memorandum of Review

STN: NDA 201849

Subject: Immunogenicity review of glucagon for injection

Review Date: 12/16/14

Submission Date: 9/30/10

Primary Reviewer: Steven Bowen, PhD, OBP

Secondary Reviewer: Susan Kirshner PhD, OBP

RPM: Elisabeth A. Hanan, M.S.

Applicant: Fresenius Kabi USA, LLC

Product: Glucagon for injection

Indication: [REDACTED] ^{(b) (4)} for use as a diagnostic aid during radiologic examinations.

Recommendation –

No post-marketing requirement to assess glucagon immunogenicity is needed at this time.

Justification -

Glucagon is a 29 amino acid polypeptide hormone produced by pancreatic alpha cells. It raises blood glucose levels through the depolymerization of glycogen in the liver. It is also effective in relaxing the bowel for gastrointestinal examinations. In 1998 the FDA approved the use of recombinant glucagon for the treatment of severe hypoglycemia and for diagnostic use (Novo Nordisk Pharmaceuticals Inc., NDA #020918, approved 6/22/98 and Eli Lilly and Company, NDA# 020928, approved 9/11/98). As part of NDA#

020928 Novo Nordisk Pharmaceuticals Inc. conducted a parallel, randomized study to assess immunogenicity of both recombinant and animal-source glucagon in 75 subjects (study H3F-MC-GFAB). The study, conducted between October 1996 and February 1997, involved 3 intramuscular injections of recombinant (N=50) or animal-source (N=25) glucagon 3 weeks apart. Anti-glucagon antibody levels at baseline and at 6-weeks following the final injection were below the limit of detection for both treatment groups.^{1,2}

Rare hypersensitivity reactions following the administration of animal-source and recombinant glucagon for gastrointestinal exams have been reported. Symptoms included hives, periorbital edema, erythema multiforme, and respiratory distress^{3,4,5,6}. In some cases anaphylaxis requiring epinephrine injection also occurred⁴. Most reported incidents have been immediate, however one case of delayed hypersensitivity, manifesting 1 day after glucagon injection, has been reported⁵. The role of glucagon as the allergen in these cases was speculative, as glucagon was typically co-administered with other potentially allergenic factors and confirmatory drug re-challenges were not performed.

Diabetic patients receiving insulin therapy have, in some cases, developed neutralizing antibodies to glucagon^{7,8}. This is possibly due to glucagon contamination in the insulin drug product, carried over from the pancreatic extract used in the manufacturing process at the time that these studies were conducted. In this circumstance, exogenous glucagon administered through insulin therapy may have elicited an antibody response. However, it is difficult to determine whether other impurities in the insulin drug product may have acted as an adjuvant to induce the glucagon-specific antibodies in these patients.

Animal studies have demonstrated very low immunogenicity of purified glucagon. In one such study rabbits, guinea pigs and mice were injected with purified animal-source glucagon with or without an adjuvant (CFA or Alum)⁹. The parameters used to measure immunogenicity were anaphylaxis, Arthus reaction and the presence of glucagon-specific antibodies. The results indicated that, unless an adjuvant was present in the injection, the purified glucagon had very weak immunogenicity by all parameters

¹ http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20928.pdf

² <http://www.lillytrials.com/results/glucagon.pdf>

³ Edell SL. *AJR Am J Roentgenol.* 1980 Feb;134(2):385-6.

⁴ Gelfand DW et al. *AJR Am J Roentgenol.* 1985 Feb;144(2):405-6.

⁵ Neoh CY et al. *Ann Acad Med Singapore.* 2006 Apr;35(4):279-81.

⁶ Herskovitz PI et al. *Radiology.* 1997 Mar;202(3):879.

⁷ Cresto et al. *Lancet.* 1974 ;1(7867):1165.

⁸ Villalpando et al. *Diabetes.* 1979 (4):294-9.

⁹ Kasama et al. *Tohoku J. exp. Med.*, 1983, **141**, 407-415

measured. However, when an adjuvant was present, a robust immune response to glucagon was generated, consistent with other published reports¹⁰.

Different regions of the glucagon molecule exhibit unique properties of immunogenicity in the presence of an adjuvant. This was illustrated in a study in which bovine glucagon was digested with trypsin, yielding fragments of varying size. Guinea pigs immunized with whole glucagon plus CFA were analyzed for both antibody specificity and T cell responsiveness to each peptide fragment. It was found that most of the antibodies generated to glucagon were generated against an epitope in the N-terminal region consisting of amino acids 1-17. In contrast, T cell proliferation was strongest in response to the C-terminal amino acids 18-29^{11,12}. Thus the N-terminal and C-terminal regions of the glucagon molecule contain epitopes predominantly recognized by B-cells and T-cells respectively.

Due to the weak immunogenicity of purified glucagon demonstrated in the studies outlined above, a post-marketing requirement for the sponsor to monitor immunogenicity of the glucagon drug product is not necessary.

**Steven E. Bowen -S
(Affiliate)**

Digitally signed by Steven E. Bowen -S (Affiliate)
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH,
ou=People, 0.9.2342.19200300.100.1.1=2000624627,
cn=Steven E. Bowen -S (Affiliate)
Date: 2015.03.26 09:31:41 -04'00'

Primary Reviewer: Steven Bowen, Ph.D. , Staff Fellow, CDER, OBP, Division III

**Susan L. Kirshner
-S**

Digitally signed by Susan L. Kirshner -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=1300194629,
cn=Susan L. Kirshner -S
Date: 2015.03.26 10:05:27 -04'00'

Secondary Reviewer: Susan Kirshner, Ph.D., Review Chief, CDER, OBP, Division III

¹⁰ Unger et al. *J. clin. Invest.*, 1968, **40**, 1280-1289

¹¹ Senyk et al. *Science*. 1971 Jan 29;171(3969):407-8

¹² Senyk et al. *J Exp Med*. 1971 Jun 1;133(6):1294-308.

MEMORANDUM

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

DATE: January 5, 2015

TO: Jean-Marc Guettier, M.D.
Director, Division of Metabolism and Endocrinology
Products (DMEP)
Office of Drug Evaluation II
Office of New Drugs

FROM: Xikui Chen, Ph.D., Pharmacologist
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 201849, Glucagon for
Injection, sponsored by Fresenius-Kabi, LLC

At the request of the Division of Metabolism and Endocrinology Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) audited the clinical and analytical portions of the following bioequivalence study:

Study Number: GLUC-002-CP1
Study Title: "Bioequivalence of a Test Formulation of Glucagon for SC Injection Compared to Glucagon for Injection (Bedford Laboratories) Under Fasted Conditions"

Clinical Site at West Houston Clinical Research Services:
The inspection of the clinical portion of the study was conducted by Anya D. Lockett-Evans, M.D. (ORA Investigator, DAL-DO) at West Houston Clinical Research Services, in Houston, TX, from October 23 to October 30, 2014. The audit included the

collection of reserve samples, review of informed consent forms, study protocol, reporting of adverse events, case report forms, subject records, facility personnel, standard operating procedures (SOPs), IRB approvals, protocol deviations, drug accountability records, and the receipts and storage of the medications. There were no objectionable findings during the inspection and Form FDA-483 was not issued. Discussion items included:

- 1) The change or correcting of lot numbers and expiration dates for both the test and reference drug noted on pre-printed CRFs

This reviewer notes that the changes of lot numbers and expiration dates on records, from those on the pre-printed CRF template, were not necessarily contemporaneous with the dates on documents of Dose Administration and Blood Collection. There were no dates and no initials for the changes on the CRFs. However, documents of Dose Administration and Blood Collection collected during inspection, had changes, while submitted documents in DARRTS did not have changes for subjects 11, 12, 13, 16, 17 and 18. These six subjects' records must have been changed after photocopies were made for the clinical study report. DBGLPC cannot assure that the changes were corrections, because the EIR exhibits did not include an independent contemporaneous record to confirm the changes to CRFs.

Four hundred (400) vials each for test glucagon lot# C113-002 with expiration date 4/2015, and for reference GlucaGen lot# BW60511 with expiration date 4/2014, were shipped on May 9, 2013 and received on May 10, 2013 at the clinical site. Another shipment of 400 vials each for the test glucagon with the same lot#, and for reference GlucaGen with the same lot#, was shipped on May 13, 2013 and received on May 14, 2013 at the clinical site. However, Investigational Drug Accountability forms listed 800 vials of test glucagon lot# C113-002 and 800 vials of reference lot# BW60511 and all received: 05/10/2013. Moreover, reserve samples were not labeled with the date of the received shipments, and dispensing or dosing records did not indicate the date of receipt of the individual dose unit. Please see the following text at item 3 of the Final Rule published April 28, 1993 [Federal Register Vol. 58 No. 80]:

"However, if additional supplies of the test article and of the reference standard are needed by a testing facility for additional studies, the testing facility must retain the required reserve samples from the subsequent shipment

regardless of whether the shipment is from the same batch as that previously provided to the testing facility. This is to ensure that the reserve samples are, in fact, representative of the batch provided by the study sponsor to the testing facility."

Because the units used for dosing and the reserve samples were not labeled by their shipment dates, DBGLPC cannot assure which samples represented which shipment. However, the shipping records indicate there are no differences in the products between the two shipments.

2) The mode of "sub-cutaneous" injection for both the test and reference drug products was ambiguously stated in the protocol title, but adequately addressed under section 8.0 (Objectives of the Protocol)

Section 8.0 Objectives of the Protocol expresses the intent of subcutaneous injection at a shoulder and pharmacokinetic sampling from the opposite arm. The randomization schedule dated May 8, 2013 lists the intended right or left shoulder for each SC injection. Swelling and redness were recorded on the Injection Site Inspection form, which is included in each CRF. However, the site for subcutaneous injection and the shoulder were not recorded. DBGLPC cannot assure that the drug products were administered by subcutaneous injection at the intended shoulder.

Bioanalytical Site at (b) (4)

The inspection of the bioanalytical portion of the study was conducted by (b) (4) and (b) (4) at (b) (4) in (b) (4) from (b) (4) to (b) (4). The audit included a thorough review of all records associated with the study and method validation, correspondence, records of subject sample receipt and storage, notebooks and electronic records, and SOPs, as well as inspection of facilities and interviews and discussions with the firm's management and staff. Form FDA-483 was issued for observations on study GLUC-002-CP1. (b) (4) sent responses to the Form FDA-483 observation to the (b) (4) (b) (4) USFDA, dated October 3, and December 12, 2014. The sponsor submitted an amended report to NDA 201849. None of these documents included the items 1, 2, 3, and 5 cited in (b) (4) response. The Form FDA-483 observation, (b) (4) responses and my evaluations follow:

1. You failed to accurately calculate concentrations of the analyte glucose for calibration standards, quality control samples, and 1824 study plasma samples for the assays in Study AA98483-02.

(b) (4) prepared glucose stock solution (nominally 300.000 µg/mL) by weighing approximately 0.60000 g of glucose and mixing with 2.00 mL of ultrapure water. (b) (4) did not measure the solution volume, or adjust for expansion of volume from 2.00 mL.

In (b) (4) Amendment 1 to the Bioanalytical Report for study AA98483-02, dated December 10, 2014, submitted to NDA 201849 by the sponsor, they reported a measured specific gravity (1.0967 g/ml) for the glucose stock solution. The Amendment did not describe the adjustment for specific gravity to concentration. However, DBGLPC estimates the volume of the stock solution as follows:

$$2.6 \text{ g} \div 1.0967 \text{ g/mL} = 2.3707 \text{ mL}$$

This volume contained 600 mg of glucose. Thus, the w/v glucose concentration was this:

$$600 \text{ mg} \div 2.3707 \text{ mL} = 253.08 \text{ mg/mL}$$

It appears that (b) (4) used an adjustment factor $300 \div 253.08 = 1.1854$ to change glucose concentrations throughout the amended report. DBGLPC agrees with this adjustment.

Conclusions:

Following review of the inspectional findings, I conclude that:

- The incomplete labeling of drug products from the two shipments of study drugs does not appear to have compromised the integrity of subject dosing (i.e., who got which product).
- The adjusted data for glucose concentrations in Amendment 1 to the bioanalytical final report for study AA98483-02, dated December 10, 2014, are acceptable for Agency review.
- The analytical data for glucagon concentrations in the original bioanalytical final report for study AA98483-01 dated October 31, 2013, are acceptable for Agency review.

Xikui Chen, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

**VAI - West Houston Clinical Research Services, Houston, TX
(FEI# 3006548377)**

**VAI - [REDACTED] (b) (4)
(FEI# [REDACTED] (b) (4))**

DARRTS CC:

OSI/DBGLPC/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Chen
OSI/DBGLPC/Dejernett/Nkah/Fenty-Stewart/Johnson
CDER/OND/ODEII/DMEP/Jean-Marc Guettier/Elisabeth A. Hanan

[REDACTED] (b) (4)

Draft: XC 12/30/2014

Edits: MFS 12/30/2014; SHH 12/31/2014; WHT 1/2/2015

OSI: File#: BE [REDACTED] (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites/[REDACTED] (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/West Houston Clinical Research Services, Houston, TX

FACTS: [REDACTED] (b) (4)

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/s/

XIKUI CHEN
01/05/2015

SAM H HAIDAR
01/05/2015

WILLIAM H TAYLOR
01/05/2015

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: December 23, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 201849
Product Name and Strength: Glucagon for Injection, 1 mg per vial
Submission Date: December 19, 2014
Applicant/Sponsor Name: Fresenius Kabi
OSE RCM #: 2014-1751-1
DMEPA Primary Reviewer: Sarah K. Vee, PharmD
DMEPA Associate Director: Lubna Merchant, PharmD, MS

1 PURPOSE OF MEMO

DMEP requested that we review the revised container label (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.¹

2 CONCLUSIONS

The company's proposal is acceptable from a medication error perspective.

¹ Vee S. Label and Labeling Review for Glucagon for Injection (NDA 201849). 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); 2014 NOV 3. 32 p. OSE RCM No.: 2014-1751.

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/s/

SARAH K VEE
12/23/2014

LUBNA A MERCHANT
12/23/2014

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 3, 2014
Requesting Office or Division: Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number: NDA 201849
Product Name and Strength: Glucagon for Injection, 1 mg per vial
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Fresenius Kabi
Submission Date: August 8, 2014
OSE RCM #: 2014-1751
DMEPA Primary Reviewer: Sarah K. Vee, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

Fresenius Kabi submitted a response to FDA's complete response on August 8, 2014. Division of Metabolic and Endocrinology Products (DMEP) requested that we review the submitted label and labeling for the product.

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
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant revised the container label and carton labeling according to our recommendations from our previous review except for one item (See Section 4.1). We find the revisions acceptable.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the revised container label and carton labeling are acceptable except for the listing of the NDC numbers.

4.1 RECOMMENDATIONS FOR FRESENIUS KABI

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

1. Please revise the NDC number of the vial to one which differs from that on the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Glucagon that Fresenius Kabi submitted on August 8, 2014.

Table 2. Relevant Product Information for Glucagon	
Initial Approval Date	N/A
Active Ingredient	Glucagon
Indication	Use as a Diagnostic Aid
Route of Administration	Intravenous or intramuscular
Dosage Form	Lyophilized powder for injection
Strength	1 mg/mL
Dose and Frequency	<ul style="list-style-type: none"> • (b) (4) stomach, (b) (4) and small bowel is 0.2 mg to 0.5 mg given intravenously or 1 mg given intramuscularly • (b) (4) colon is 0.5 mg to 0.75 mg intravenously and 1 mg to 2 mg intramuscularly
How Supplied	1 mg per vial in packages of 10
Storage	The glucagon for injection package may be stored up to 24 months at 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature] prior to reconstitution. Do not freeze. Keep in the original package to protect from light
Container Closure	3-mL, tubing, Type I USP glass vials, closed with (b) (4) gray (b) (4) rubber stoppers, capped with aluminum crimped, flip-cap seals (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on September 9, 2014 using the term, “Glucagon” to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified 1 previous review¹, and we confirmed that most of our previous recommendations were implemented.

¹ Wilkins Parker, J. Label and Labeling Review for Glucagon for Injection (NDA 201849). 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); 2012 Sept. 7. OSE RCM No.: 2012-218.

APPENDIX C. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Glucagon labels and labeling submitted by Fresenius Kabi on August 8, 2014.

- Container label
- Carton labeling

G.2 Label and Labeling Images

(b) (4)



² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SARAH K VEE
11/03/2014

YELENA L MASLOV
11/03/2014

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

Application: NDA 201849

Application Type: New NDA – Class 2 Resubmission

Name of Drug/Dosage Form: Glucagon for Injection
(note that the applicant does not intend to submit a proprietary name for review)

Applicant: Fresenius Kabi USA, LLC

Receipt Date: August 8, 2014

Goal Date: February 8, 2015

1. Regulatory History and Applicant's Main Proposals

This application seeks approval for Fresenius Kabi's formulation of glucagon for injection for use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract. The application was submitted via the 505(b)(2) approval pathway using Novo Nordisk's GlucaGen (NDA 020918) as the comparator listed product. The original submission date for the application was October 5, 2010, which was followed by a Refuse-to-File action taken by the Agency on December 3, 2010. The applicant resubmitted on November 30, 2011, and a Complete Response letter was issued by the Agency on September 27, 2012. The current Class 2 Resubmission of the NDA was received by the Agency on August 8, 2014. The submitted labeling includes the applicant's responses to labeling comments that were included with the Agency's Complete Response letter from the last review cycle.

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 for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix. Additional preliminary comments for the PI were prepared by Monika Houstoun, Acting Associate Director for Labeling, in conjunction with the Study Endpoints and Labeling Division (SEALD).

All SRPI format deficiencies of the PI and other labeling issues identified above were conveyed to the applicant via email on September 18, 2014 (see communication filed in DARRTS). The applicant was asked to correct these deficiencies and resubmit the PI in Word format by November 1, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-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 A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- NO** 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: Margins on left and right sides are less than 0.5-inch.
- YES** 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:
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment:
- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
Comment: 'Recent Major Changes' heading is not in all upper case letters; all else is as required.
- NO** 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 A for a sample tool illustrating white space in HL.
Comment: White space is not present above the DOSAGE AND ADMINISTRATION heading; all else is as required.
- 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. Section headings must be presented in the following order in HL:

Section	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 the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

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 in HL 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 heading in UPPER CASE, containing the word **“WARNING”** (even if more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading 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 should be centered immediately beneath the heading 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 heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- YES** 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) --- 9/2013”.

Comment:

- NO** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *The RMC that are listed presumably are from the innovator product and do not apply to this label because this product has not yet been approved. In addition, all RMCs listed are more than one year old.*

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *Per SEALD, the established pharmacologic class (EPC) “gastrointestinal motility inhibitor” is not included in the EPC list in e-list. The pharm tox reviewer was asked to request that this EPC be added to the database.*

Dosage Forms and Strengths in Highlights

N/A

Selected Requirements of Prescribing Information

20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Product only has one dosage form.*

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. 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) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. 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** 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** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. 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** 27. The same heading 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** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. 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 (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of 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** 32. 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 Labor and Delivery
8.3 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:

- NO** 33. 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)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: Section 2.2 references "Pharmacodynamics (12.2)" instead of "Clinical Pharmacology (12.2)". All else is as required.

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: Listed RMC in the HL are not applicable and should be deleted.

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION**". This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state "None."

Comment: Contraindications are listed.

ADVERSE REACTIONS Section in the FPI

- N/A** 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"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: No clinical trials data are included in the label.

- N/A** 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), 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: No postmarketing adverse reaction data are included in the label.

PATIENT COUNSELING INFORMATION Section in the FPI

N/A

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *No patient labeling was submitted with this NDA.*

- N/A**
42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) 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: *No patient labeling was submitted with this NDA.*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 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

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 [text]

14.2 [text]

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/

ELISABETH A HANAN
09/18/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 7, 2012

Acting Team Leader: Jamie Wilkins Parker, Pharm.D.
**Division of Medication Error Prevention
and Analysis**

Deputy Director: Kellie Taylor, Pharm.D., MPH
**Division of Medication Error Prevention
and Analysis**

Drug Name(s) and Strength(s): Glucagon for Injection, 1 mg/mL

Application Type/Number: NDA 201849

Applicant/sponsor: APP Pharmaceuticals, Inc.

OSE RCM #: 2012-218

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DRAFT

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Glucagon, NDA 201849 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

This product is a 505b(2) referencing GlucaGen. The Application was re-submitted to the agency on November 30, 2011 after an initial refusal to file in 2010. This product is (b) (4) seeking an indication of a diagnostic agent, and not an indication for emergency treatment of severe hypoglycemia. (b) (4)

An Information Request was sent to the Applicant on June 7, 2012, inquiring whether or not they intended to pursue a proprietary name for their product, as well as to provide label and labeling suggestions from the Agency subsequent to a conference call which occurred June 1, 2012. During the conference call the Agency expressed concerns (b) (4)

In their response, the firm agreed to only market a carton of ten vials of Glucagon powder for reconstitution, (b) (4)

The re-submitted carton labels and container labeling are the subjects of this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the June 29, 2012 labeling submission.

- Active Ingredient: Glucagon for Injection
- Indication of Use: Gastrointestinal motility inhibitor for use as a diagnostic aid
- Route of Administration: Intramuscular or Intravenous
- Dosage Form: lyophilized powder
- Strength: 1 mg/mL
- Dose and Frequency: Varies per diagnostic use from 0.2 mg to 2 mg
- How Supplied: 10 pack of vials (no diluent included)
- Storage: 68°-77° F

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 29, 2012 (Appendix A)
- Carton Labeling submitted June 29, 2012 (Appendix B)
- Insert Labeling submitted June 29, 2012

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our risk assessment of the Glucagon product design as well as the associated label and labeling.

4 CONCLUSIONS

DMEPA concludes that the warnings included on the proposed container labels and carton labeling adequately differentiate this product from those glucagon products approved for the treatment of hypoglycemia. However, we find that changes are needed to the information displayed on the labels and labeling.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label

1. Relocate the statement “For Diagnostic Use Only” to the principal display panel of the vial, and revise to state “For Diagnostic Use Only, Not Approved to Treat Hypoglycemia.”
2. Please revise the strength statement to state “1 mg per vial ”, and relocate the net quantity statement to a different location on the principal display panel, away from the strength statement, so that they are not confused.
3. We wonder if the statement “Glucagon as Hydrochloride 1 mg (b)(4)” is necessary. We suggest deleting the statement if it is not needed. If it is needed, we suggest relocating to the side panel of the label, and revise to state “Glucagon as Hydrochloride 1 mg” (b)(4)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4. Please revise the NDC number of the vial to one which differs from that on the carton labeling.

B. Carton Labeling

1. Please revise the strength statement to state “1 mg per vial”, and relocate the net quantity statement to a different location on the principal display panel, away from the strength statement, so that they are not confused.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

DRAFT

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: Container Labels



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/s/

KELLIE A TAYLOR on behalf of JAMIE C WILKINS PARKER
09/07/2012

KELLIE A TAYLOR
09/07/2012

MEMORANDUM

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

DATE: August 27, 2012

TO: Mary H. Parks, M.D.
Director,
Division of Metabolism and Endocrinology Products,
Office of Drug Evaluation II

FROM: Young Moon Choi, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations;

And

William H. Taylor, Ph.D.
Division Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 201-849, Glucagon for
Injection, 1 mg (1 IU/ml) sponsored by APP
Pharmaceuticals

At the request of the Division of Metabolism and Endocrinology Products (DMEP), Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: 20090101

Study Title: "Bioequivalence of a Test Formulation of Glucagon for Injection, 1 mg (1 IU/mL) (manufactured by APP pharmaceuticals) compared to GlucaGen® 1 mg (1 IU/mL) Manufactured by Bedford Laboratories Under Fasted Conditions"

The clinical portion of the study was inspected by Darla J. Christopher (ORA) from 7/16/2012 to 7/20/2012 at West Houston Clinical Research Services Houston, TX. The inspection included a thorough examination of study records, facilities, and equipment, and interviews and discussions with the firms' management and staff. Following the inspection, Form FDA 483 containing one inspectional observation was issued (**Attachment 1**). The firm's response to the Form FDA 483 has not been received as of this writing. An addendum to DBGLPC evaluation will be forwarded to DMEP upon receipt of the response. DBGLPC reviewer's evaluation of inspectional observation follows:

Observation 1.

An investigation was not conducted in accordance with the investigational plan. Specifically, Record for reconstituting the product states to inject the subject within approximately 15 minutes of reconstitution. The manufacturer's insert instruction sheet states to use reconstituted product immediately. The shortest time period between reconstitution and injection was 21 minutes for all four periods. The longest time period between reconstitution and injection was 41 minutes for all four periods.

The firm provided documents demonstrating three-day stability of glucagon after reconstitution at 25°C (**Attachment 2**) to the ORA investigator at the conclusion of inspection. The longest duration between glucagon reconstitution and injection during the study was 41 min and within the established duration of stability. Therefore, this reviewer is of the opinion that observation 1 is not likely to significantly impact study results.

The analytical portion of glucagon measurement of the study was inspected by [REDACTED] (b)(4)

At the conclusion of the inspection, there were no significant inspectional observations and a Form FDA 483 was not issued.

CONCLUSION:

This reviewer recommends that the glucagon data from the Study 20090101 should be accepted for Agency review.

(b) (4)

Final Classifications:

VAI - Clinical Site: West Houston Clinical Research Services
Houston, Texas, USA (FEI: 3007853991)

NAI - Analytical Site: (b) (4) (FEI:
(b) (4))

CC:

CDER OSI PM TRACK

OSI/DBGC/Taylor/Haidar/Skelly/Biswas/Choi/Dejernett/CF

OND/ODEII/DMEP/Jairath

OTS/OCP/DCPII/Zadezensky

(b) (4)/Bromley (DIB)/Bous (BIMO)/Dixon/Peterson

DAL-DO/Turcovski (DIB)/Martinez/Bias (BIMO)/Cheney/Christopher

Draft: YMC 8/27/2012

Edit: GB 8/27/2012, 8/28/2012

OSI File: BE (b) (4); O:\BE\assigns\bio201849.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good
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FACTS: (b) (4)

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YOUNG M CHOI
09/03/2012

WILLIAM H TAYLOR
09/04/2012