CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201849Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201849

COMPLETE RESPONSE

Fresenius Kabi USA, LLC.
Attention: Heidi Guzalo
Senior Manager, Regulatory Affairs
1501 E Woodfield Road, Suite 300 East
Schaumburg, IL 60173

Dear Ms. Guzalo:

Please refer to your New Drug Application (NDA) dated October 5, 2010, received October 5, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Glucagon for Injection.

We acknowledge receipt of your amendments dated October 18 and 25, and December 30, 2010, January 28, March 2 and 9, November 30, 2011, and May 16, 18, and 31 (2), June 27 and 29, and September 12, 2012.

Your submission dated November 30, 2011, constituted a resubmission following our December 3, 2010, refuse-to-file letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

We found significant deficiencies in the bioanalytical assay for glucose and therefore, the pivotal bioavailability study 200090101 titled "Bioequivalence of a Test Formulation of Glucagon for Injection, 1 mg (1 IU/mL) manufactured by Fresenius Kabi USA, LLC.) compared to GlucaGen 1 mg (1 IU/mL) injection (manufactured by Novo Nordisk) Under Fasted Conditions" is not acceptable. Fresenius Kabi USA used a conventional diagnostic test procedure with single-concentration calibration for the glucose measurements. This method is not compliant with 21 CFR 320.29(a) and not consistent with the methodology recommended by Guidance for Industry: Bioanalytical Method Validation (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf). Thus, the glucose measurements are not reliable. Of note, an information request during the course of the review revealed that the investigators did not retain plasma samples for glucose reanalysis. Therefore, a glucose re-assay of the samples using a validated method to potentially address this bioanalytical deficiency was not possible.

In order to address these deficiencies, another bioequivalence study will need to be conducted.

FACILITY INSPECTIONS

During a recent inspection of the Fresenius Kabi USA (3159 Staley Rd, Grand Island, New York) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

We have the following recommendations for the labeling.

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. 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, to better distinguish between these two statements.

3. We question 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)

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

B. *Carton Labeling*

5. 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, to better distinguish between these two statements.

C. *Package Insert*

6. Add an "Important Limitation of Use" as follows: "This product is not intended for use to treat severe hypoglycemia because it is not packaged with a syringe and diluent necessary for rapid administration during an emergency."

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your

lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MARY H PARKS
09/27/2012