



NDA 217724/Original 1

**COMPLETE RESPONSE**

Zealand Pharma US, Inc.  
Attention: Christopher R. DeFusco, PhD  
Head of US Regulatory Affairs  
50 Milk Street, 16<sup>th</sup> Floor  
Boston, MA 02109

Dear Dr. DeFusco:

Please refer to your new drug application (b) (4)

or dasiglucagon injection.

We acknowledge receipt of your amendment dated (b) (4) which constituted a complete response to our (b) (4) action letter.

NDA 217724 provides for the use of dasiglucagon injection for the following indications which, for administrative purposes, we have designated as follows:

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The subject of this action letter is NDA 217724/Original 1. (b) (4)

All future submissions to NDA 217724/Original 1 and NDA 217724/Original 2 should specify the NDA number and the Original number to which each submission pertains.

We have completed our review of NDA 217724/Original 1 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.

**FACILITY INSPECTIONS**

Following a current good manufacturing practice (CGMP) inspection of (b) (4)

listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these

deficiencies to the FDA office indicated on the FDA 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your pending application, therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a pre-approval inspection (PAI) of the facility. Satisfactory outcomes of both the PAI and the CGMP surveillance inspections will be needed prior to an approval of the application. As the Applicant, we do not expect a response to this facility related deficiency when responding to any other deficiencies cited in this or other letters, instead, please work with the facility, as applicable, in resolving the related deficiencies.

### **PRESCRIBING INFORMATION**

Submit draft labeling that is responsive to our electronic communication dated

(b) (4)

Prior to resubmitting the labeling, use the Selected Requirement of Prescribing Information (SRPI) checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.<sup>1</sup>

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources<sup>2</sup> and Pregnancy and Lactation Labeling Final Rule<sup>3</sup> websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

<sup>3</sup> <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
  - Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The SRPI – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Additional resources for the PI, patient labeling, and carton/container labeling.

### **PROPRIETARY NAME**

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

### **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described in 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 (AE), serious adverse events (SAE), and common AEs, 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 AE 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 AEs occurring in clinical trials.

- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the dropouts from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an AE. In addition, provide narrative summaries for SAEs.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious AEs 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 the 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.

### **ADDITIONAL COMMENTS**

We have the following comments and requests for additional information that are not approvability issues. However, we request you submit your responses with your complete response to this letter.

- (1) We note that age and body weight are covariates for dasiglucagon exposure. The lowest body weight enrolled in study 17103 was 4.1 kg. Therefore, no clinical data was generated for infants < 4.1 kg.
  - You have not described any information regarding body weight in *Section 2 Dosage and Administration* of the submitted draft PI. Clarify how prescribers should consider body weight when determining the dose of dasiglucagon. Submit your proposal (i.e., draft PI language) and justification with supporting data for *Section 2 Dosage and Administration* regarding the impact of age and body weight on dasiglucagon dosing.

Furthermore, we note that the simulated 95% confidence interval (CI) upper limit of dasiglucagon exposures (based on 70 microgram/hour dose) for body weight < 4.1 kg is anticipated to exceed the peak plasma exposure of 3.78 nmol/L at the no observed adverse effect level (NOAEL) for the transient freezing absences in rats. Provide a justification with clinical safety data to support a dosing recommendation for infants < 4.1 kg.

(2) You propose to limit the indication statement based on chronological age i.e., to pediatric patients with CHI who are at least 7 days old.

- We note that study 17103 excluded infants with chronological age < 7 days. Clarify whether you anticipate any differences in the overall benefit/risk assessment in infants < 7 days of age (including premature infants) as compared to those  $\geq$  7 days of age.
- Clarify if you are proposing to include premature and term infants in the proposed indication.
- We note that study 17103 excluded subjects < 34 weeks of gestational age. Clarify if any premature infants were enrolled in study 17103.

(3) Comment on safety and efficacy considerations in small for gestational age (SGA) and premature infants compared to term infants. Specifically, address the following:

- Provide information on the impact of incomplete kidney development and immature kidney physiology in premature infants on dasiglucagon pharmacokinetic (PK) characteristics compared to term infants with similar body weight.
- Provide information on the impact of possible limited hepatic glycogen stores in SGA and premature infants on efficacy of continuous subcutaneous (SC) administration of dasiglucagon up to 3 weeks.
- Provide your justification for safety of continuous SC administration of dasiglucagon up to 3 weeks in SGA and premature infants. Clarify how the safety profile of dasiglucagon may differ between SGA and premature and term infants and if SGA and premature infants may be at increased risk of drug-related AEs due to physiologic immaturity. For example, we note that AEs of hyponatremia, thrombocytopenia and metabolic acidosis have been described in the literature as possibly associated with the off-label use of glucagon products in premature and low birth weight infants<sup>4</sup>.

In addition, provide your justification for safety of dasiglucagon in infants < 4.1 kg considering the simulated 95% CI upper limit of dasiglucagon exposures (based on 70 microgram/hour dose) for body weight < 4.1 kg is anticipated to exceed the peak plasma exposure of 3.78 nmol/L at NOAEL for the transient freezing absences in rats.

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<sup>4</sup> Belik J, et al. Pediatrics. 2001 Mar;107(3):595-7; Charsha DS, et al. Pediatrics. 2003 Jan;111(1):220-1; Hoban R, et al. Paediatr Child Health. 2022 Sep 8;28(1):24-29.

- Provide any other data and information related to the above request.
- (4) Provide a justification for use of the infusion pump and infusion set in infants < 4.1 kg, including in premature infants. Clarify if you anticipate any technical challenges in inserting and/or maintaining the infusion pump and infusion set in lower weight or premature infants due to limited SC fat.
- (5) The effect of moderate to severe renal impairment on dasiglucagon PK has not been investigated. Submit your proposal for the product PI regarding renal impairment with justification and supporting data.

### **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 in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference 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 draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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, contact

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Sincerely,

*{See appended electronic signature page}*

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Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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