NDA 212097/S-012

COMPLETE RESPONSE

Xeris Pharmaceuticals, Inc.
Attention: Michele Yelmene
Vice President, Global Regulatory Affairs & Operations
1375 West Fulton Street, Suite 1300
Chicago, IL 60607

Dear Michele Yelmene:

Please refer to your supplemental new drug application (sNDA) dated and received April 10, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Gvoke (glucagon) injection.

We also acknowledge receipt of your amendment dated January 4, 2024, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

This "Prior Approval" efficacy supplement to your application provides for addition of a new indication as a diagnostic aid for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract in adult patients.

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 AND BIOPHARMACEUTICS

1. Your application does not contain an adequate scientific bridge between your proposed to-be-marketed product and the relied-upon listed drug for the proposed indication by IV administration. Because your proposed product does not contain the same inactive ingredients in the same concentration as the relied-upon listed drug, a biowaiver cannot be granted based on 21 CFR 320.22(b).

   (b) (4) did not demonstrate comparable bioavailability of the XP-9164 product to the relied-upon listed drug, Fresenius Kabi's glucagon product (NDA 201849), following a single intravenous (IV) dose of 0.75 mg. (b) (4)

[redacted] (b) (4) A nonclinical PK study is not sufficient to establish an adequate scientific bridge.

To resolve this deficiency, you must establish an adequate scientific bridge between your proposed to-be-marketed product and the relied-upon listed drug for the proposed indication by IV administration.

You may establish an adequate scientific bridge by conducting a new a pharmacokinetics (PK) study in humans that demonstrates comparable bioavailability of your proposed product and the relied-upon listed drug for IV administration.

OR, in lieu of a PK study that demonstrates comparable bioavailability, a scientific bridge sufficient to demonstrate comparable bioavailability may be acceptable under 21 CFR 320.24(b)(6) if you provide an adequate justification that the differences in formulation of your proposed product will not affect the PK and the *in vivo* performance of your proposed product in comparison to the relied-upon listed drug.

In support of establishing a scientific bridge pursuant to 21 CFR 320.24(b)(6), you should submit a side-by-side comparison on three batches of your proposed product and the relied-upon listed drug including:

i. A side-by-side comparison table of the formulation (qualitative and quantitative composition, volume, etc.) before and after reconstitution (or dilution, as applicable) for the proposed product and the relied-upon listed drug.

ii. Comparative physicochemical data (appearance, pH, osmolality, relative density, glucagon assay, total impurities, total glucagon degradants, total glucagon aggregate) before and after reconstitution (or dilution, as applicable) for the proposed product and the relied-upon listed drug. The measurements should be performed in triplicate for each lot tested.

iii. A justification for any differences in the formulation and dosing of the proposed product relative to the relied-upon listed drug. The justification should demonstrate that, for each difference, the *in vivo* performance (i.e., PK, clinical safety, or clinical efficacy) would be unaffected. For example, your justification would need to adequately address clinical concerns that the presence of DMSO in your formulation and/or the hypertonicity of the IV infusion may affect PK through effects on the peripheral venous endothelial cells. You may include literature data and/or your study reports to support your scientific bridge.

iv. Information and data of comparative dose accuracy testing between your proposed product and the relied-upon listed drug supporting complete dose delivered of glucagon without submicron particle formation events prior to administration as provided in the labeling. Dose accuracy testing may be examined by glucagon content assay in a diluted solution collected after delivery via syringes with needles. Dynamic light scattering analysis may be used to determine submicron particles in a diluted glucagon solution after delivery.

We strongly recommend that you discuss the acceptability of your bridging strategy with the Agency by requesting a meeting prior to resubmitting your application.

CHEMISTRY, MANUFACTURING AND CONTROLS

2. The data provided in the supplement do not support compatibility and stability of the proposed IV administration. Compatibility studies following dilution were provided for the XP-9164 formulation under IND 156281. Provide admixture studies using your proposed formulation (Gvoke vial, rather than XP-9164) to inform drug product compatibility and stability for the proposed dosing and administration technique (i.e., as provided in the labeling Section 2.4). These studies should include comparative gelling and agglomeration studies using the Gvoke vial formulation with the relied-upon listed drug.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, September 14, 2023, which addresses the proposed proprietary name, Gvoke VialDx. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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 in the original submission.
- Present tabulations of the new safety data combined with the supplemental application data.
- Include tables that compare frequencies of adverse events in the supplemental application 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 subject 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 supplemental application 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 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*[4].

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, contact Georgia Rogers, Regulatory Project Manager, at Georgia.Rogers@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Deputy Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

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.

/s/

PATRICK ARCHDEACON
02/09/2024 03:15:49 PM