BLA 125513/S-018

SUPPLEMENT APPROVAL

Alexion Pharmaceuticals, Inc.
Attention: Mary Lyons, RAC
Associate Director, Global Regulatory Affairs
121 Seaport Boulevard
Boston, MA 02210

Dear Ms. Lyons:

Please refer to your supplemental biologics license application (sBLA), dated August 13, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Strensiq (asfotase alfa) for injection.

This Prior Approval supplemental biologics application provides for an update to the product labeling based on long-term efficacy and safety data from patients treated in Study 1 (ENB-002-08), Study 2 (ENB-010-10), and Study 3 (ENB-006-09/ENB-008-10), which were completed after the original BLA approval, as well as labeling updates based on postmarketing reports..

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] 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.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Strensiq (asfotase alfa) for injection was approved on October 23, 2015, we have become aware of postmarketing reports in patients with hypophosphatasia (HPP) treated with Strensiq (asfotase alfa) for injection that raised the concern of a potential serious risk of loss of the product's pharmacologic action, including reduced effectiveness, which can lead to decreased survival, need for ventilatory support, rickets, fractures, and failure to thrive. These postmarketing reports include treated patients who experienced progression of HPP-associated clinical manifestations, worsening in disease-associated laboratory biomarkers (e.g., elevation in PLP) and radiographic changes showing disease progression after an initial period of clinical response. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess and

characterize the signal of this serious risk of decreased survival, need for ventilatory support, rickets, fractures, and failure to thrive.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2949-6 Observational study to evaluate the potential serious risk of hypophosphatasia (HPP)-associated early death and serious morbidity (e.g. need for ventilatory support, rickets, fractures, failure to thrive) that may result from immune-mediated loss of pharmacological effect, including reduced effectiveness, of Strensiq (asfotase alfa) in patients with HPP (perinatal/infantile-onset and juvenile-onset) enrolled as part of the Global HPP Registry. At least 30 patients (of whom at least 15 will have perinatal/infantile-onset HPP and at least 10 will be treatment-naive at enrollment) will be followed prospectively with pre-specified longitudinal assessments for at least 5 years from study enrollment and at least 200 patients (followed within the Global HPP registry) will be retrospectively evaluated for potential immune-mediated loss of pharmacologic effect (including reduced effectiveness) based on biochemical, imaging, and clinical markers of response to treatment. At baseline, all patients will have CRIM status and genotype assessed. The prospective longitudinal assessments will include at a minimum: (1) plasma asfotase alfa concentrations; (2) antidrug antibody (ADA) and neutralizing antibody (Nab) levels (and titers if appropriate); (3) plasma PPi and PLP; (4) imaging evaluation for HPP-related rickets and fractures; (5) weight and height z-scores; (6) vital status (survival, invasive ventilation-free survival); and (7) occurrence of serious adverse events including serious hypersensitivity reactions and anaphylaxis (according to NIAID/FAAN criteria). The frequency and timecourse of immune-mediated loss of effectiveness of Strensiq will be evaluated and correlated with antibody levels (and titers), CRIM status, Strensiq dosage regimen, patient's age at start of treatment, and HPP subtype.

The timetable you submitted on June 9, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2021
Final Protocol Submission:	08/2021
Interim Report:	09/2023
Interim Report:	09/2024

Interim Report:	09/2025
Interim Report:	09/2026
Interim Report:	09/2027
Study Completion:	07/2028
Final Report Submission:	01/2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess and characterize the signal of a serious risk of immune-mediated loss of pharmacologic effect, including reduced effectiveness, and evaluate strategies to mitigate this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2949-7 Single-arm, open-label clinical trial to assess different immune tolerance induction (ITI) strategies in patients with hypophosphatasia (HPP) who have demonstrated biochemical and/or clinical evidence of immune-mediated reduced therapeutic response to Strensiq (asfotase alfa). These immune tolerance induction strategies (such as short course(s) of immunosuppressive medications) will be evaluated in patients with evidence of reduced effectiveness (from PMR 2949-6) for their ability to overcome the immune-mediated loss of pharmacologic effect and mitigate the serious risk of reduced effectiveness with long-term treatment. All clinical, imaging, and biochemical HPP-associated parameters (as described under PMR 2949-6), pharmacokinetic (PK) parameters, anti-drug antibody and neutralizing antibody levels/titers, and serious adverse events (including anaphylaxis) should be monitored at pre-specified time intervals. In this clinical trial, at least 8 patients with HPP (at least 3 patients with perinatal/infantile-onset HPP) should be evaluated over at least 2 years from their trial enrollment.

The timetable you submitted on June 9, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12 /2021
Final Protocol Submission:	08 /2022
Interim Report:	08 /2024

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Interim Report:	08 /2026
Trial Completion:	08 /2027
Final Report Submission:	02 /2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 100619, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[8]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Nicolas Kong, Regulatory Project Manager at Nicolas.Kong@fda.hhs.gov or 240-402-0269.

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[8] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp

Sincerely,

{See appended electronic signature page}

Patroula Smpokou, M.D., FACMG
Deputy Director (Acting)
Division of Rare Diseases and Medical Genetics (DRDMG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Instructions for Use

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/

PATROULA I SMPOKOU
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