CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214938Orig1s000

Trade Name:	Voxzogo for injection
Generic or Proper Name:	vosoritide
Sponsor:	BioMarin Pharmaceutical, Inc.
Approval Date:	November 19, 2021
Indication:	to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses.

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APPROVAL LETTER

NDA 214938

CORRECTED ACCELERATED APPROVAL

BioMarin Pharmaceutical, Inc.
Attention: Hanna H. Cho, PhD, RAC
Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Dr. Cho:

Please refer to your new drug application (NDA) dated and received August 20, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Voxzogo (vosoritide) for injection.

This NDA provides for the use of Voxzogo (vosoritide) for injection to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses.

We acknowledge receipt of your major amendment dated March 31, 2021, which extended the goal date by three months.

We also refer to our accelerated approval letter dated November 19, 2021, which contained an error in the Instructions for Use (IFU) attachment. The following text was missing above the illustration in Step 6 of the IFU:

> ***Gently swirl*** *the vial until the powder has completely dissolved and the solution is clear.* ***Do not shake.***

This corrected action letter incorporates the correction of the error. The effective action date will remain November 19, 2021, the date of the original letter.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1]

Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, text for the Patient Package Insert, and Instructions for Use). 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]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214938**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Voxzogo (vosoritide) for injection shall be 24 months from the date of manufacture when stored at 2 to 8 °C.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 214938. All correspondences related to this voucher should refer to this tracking number.

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[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.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review.

The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

    - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),

    - the estimated demand in the U.S. for the product, and

    - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trial(s) to verify and describe clinical benefit. You are required to conduct such a clinical trial with due diligence. If the postmarketing clinical trial fails to verify clinical benefit or is not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 14, 2021. This requirement, along with required completion dates, is listed below.

4134-1 Conduct an open-label, external-controlled trial in subjects with achondroplasia (ACH) 5 years of age and older with open epiphyses to measure the effect of vosoritide on final adult height. The trial should also evaluate disproportionality and bone age as secondary endpoints. The safety endpoints related to the drug (e.g., blood pressure) or to the disease itself that may improve or worsen with long-term treatment (e.g., neurological complications, bone deformities, sleep apnea) should also be included. The total exposure to vosoritide for each patient should be sufficient to meet the study's stated objectives. The vosoritide-treated trial population should include subjects who are already enrolled and treated with vosoritide in Studies 111-202[4] /205[5], and 111-301[6] /302[7] and/or treatment-naïve subjects with a genetically confirmed ACH diagnosis.

Draft Protocol Submission:	03/2022
Final Protocol Submission:	09/2022
Trial Completion:	11/2024
Final Report Submission:	08/2025

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs
[4] A Phase 2, Open Label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with Achondroplasia
[5] A Phase 2, Open-Label, Extension Study to Evaluate the Long-Term safety, Tolerability, and Efficacy of BMN 111 in Children with Achondroplasia
[6] A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with Achondroplasia
[7] A Phase 3, Open-Label Lon-Term Extension Study to Evaluate the Safety and Efficacy of BMN 111 in Children with Achondroplasia

Submit clinical protocols to your IND 111299 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

Under 21 CFR 314.55, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.55, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[8]

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[9]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[8] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[9] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

If you have any questions, call Linda Galgay, Senior Regulatory Project Manager, at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use

  Carton and Container Labeling

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/

LISA B YANOFF
12/15/2021 04:02:56 PM