



BLA 761052

BLA APPROVAL

BioMarin Pharmaceutical Inc.
Attention: Lisa Malandro, MBA
Executive Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Malandro:

Please refer to your Biologics License Application (BLA) dated and received May 27, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Brineura (cerliponase alfa) injection, 30 mg/ mL.

We acknowledge receipt of your major amendment dated August 29, 2016, which extended the goal date by three months.

LICENSING

We have approved your BLA for Brineura (cerliponase alfa) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Brineura under your existing Department of Health and Human Services U.S. License No. 1649. Brineura is indicated to slow the progression of loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture cerliponase alfa drug substance at BioMarin Pharmaceutical Inc. in Novato, California. The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4). You may label your product with the proprietary name, Brineura, and will market it in 150 mg/ 5mL (30 mg/ mL) single-dose vials.

DATING PERIOD

The dating period for Brineura (cerliponase alfa) shall be 24 months from the date of manufacture when stored at -20 ± 5 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Brineura (cerliponase alfa) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Brineura, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

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 text.

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at

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

Content of labeling must be identical to the enclosed labeling (text for the package insert).

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on December 22, 2016, and vial and administration kit carton labels submitted on February 13, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels 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

(May 2015)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved BLA 761052.**” Approval of this submission by FDA is not required before the labeling is used.

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 Federal Food, Drug, and Cosmetic Act (FDCA). This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761052. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) 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 at <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf> (see

Section 908 of FDASIA on pages 1094-1098 which amends the FDCA by adding Section 529). Formal guidance about this program will be published in the future.

ADVISORY COMMITTEE

Your application for Brineura (cerliponase alfa) was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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.

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 signals of serious risks of hypersensitivity reactions, cardiovascular adverse events, device related complications, and adverse effects on patient performance on the CLN2 motor and language scales resulting from use of Brineura (cerliponase alfa). Additionally, these reports are not sufficient to assess signals of serious risk related to the development of neutralizing anti-drug antibodies to Brineura (cerliponase alfa).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

- 3207-1 Conduct an observational post approval safety study (Study 190-501) to evaluate the long-term safety of Brineura (cerliponase alfa) in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease), and further assess the occurrence of serious hypersensitivity reactions (including anaphylaxis), serious cardiovascular adverse events, and serious device related complications in patients followed for a minimum of ten years. In addition, this study will evaluate the effects of serious

adverse events on patient performance on the CLN2 motor and language clinical scales.

The timetable you submitted on April 26, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2017
Interim Report Submission:	06/2018
Interim Report Submission:	06/2019
Interim Report Submission:	06/2020
Interim Report Submission:	06/2021
Interim Report Submission:	06/2022
Interim Report Submission:	06/2023
Interim Report Submission:	06/2024
Interim Report Submission:	06/2025
Interim Report Submission:	06/2026
Interim Report Submission:	06/2027
Interim Report Submission:	06/2028
Interim Report Submission:	06/2029
Interim Report Submission:	06/2030
Interim Report Submission:	06/2031
Interim Report Submission:	06/2032
Interim Report Submission:	06/2033
Interim Report Submission:	06/2034
Interim Report Submission:	06/2035
Study Completion:	06/2036
Final Report Submission:	06/2037

3207-2 Develop and validate a cellular uptake assay with sensitivity adequate to evaluate the neutralizing capacity of anti-drug antibodies of Brineura (cerliponase alfa) detected in patient serum and CSF samples.

The timetable you submitted on April 26, 2017, states that you will conduct this study according to the following schedule:

Study Completion:	10/2018
Final Report Submission (including Assay Validation Report/SOP):	12/2018

3207-3 Develop and validate an assay to measure the capacity of anti- drug antibodies detected in the patient serum and CSF samples to neutralize Brineura (cerliponase alfa) enzymatic activity using conditions mimicking a lysosomal environment.

The timetable you submitted on April 26, 2017, states that you will conduct this study according to the following schedule:

Study Completion:	10/2018
Final Report Submission (including Assay Validation Report/SOP):	12/2018

3207-4 Conduct an immunogenicity study to evaluate the relationship between Brineura (cerliponase alfa) treatment and neutralizing anti-drug antibody (ADA) status. ADA-positive serum and CSF samples detected in Studies 190-201 and 190-202 will be re-tested with validated neutralizing antibody assays (developed in PMRs 3207-2 and 3207-3) for enzyme neutralization and cellular uptake, and patient serum and CSF samples will be collected and analyzed for immunogenicity assessment in Study 190-203.

The timetable you submitted on April 26, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2018
Study Completion:	06/2023
Final Report Submission:	12/2023

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected risks of serious hypersensitivity reactions, serious device related complications, and serious adverse effects on patient performance on the CLN2 motor and language scales with short-term use of Brineura (cerliponase alfa), particularly in patients below the age of 2 years.

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

3207-5 Conduct a clinical trial (Study 190-203) to evaluate the short-term safety of Brineura (cerliponase alfa) in CLN2 patients below the age of 2 years. The trial will assess the risks of serious hypersensitivity reactions, and serious device related complications with short-term use. Perform a root-cause analysis on any device related complications and/or failures including, but not limited to, an analysis of the material integrity of the intraventricular access device reservoir. In addition, this trial will evaluate the effects of serious adverse events on patient performance on the CLN2 motor and language clinical scales.

The timetable you submitted on April 26, 2017 states that you will conduct this trial according to the following schedule:

Final Protocol Submission	07/2017
Interim Report Submission:	12/2018
Interim Report Submission:	12/2019
Interim Report Submission:	12/2020
Interim Report Submission:	12/2021
Trial Completion:	12/2022
Final Report Submission:	12/2023

Submit clinical protocols to your IND 122472 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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).”**

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3207-6 For patients in Studies 190-501 and 190-203, obtain a blood sample prior to cerliponase alfa treatment to determine TPP1 enzyme activity at baseline and collect *TPP1* genotype information. Evaluate the association of enzyme activity with efficacy and safety data from PMRs 3207-1 and 3207-5. Derive the predicted protein function from the *TPP1* genotype for each patient, and compare efficacy and safety in patients with different *TPP1* genotypes based on their predicted protein function. In addition, perform similar analyses using a combined dataset from 4 clinical studies, including Studies 190-203, 190-501, 190-201 and 190-202.

The timetable you submitted on April 26, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2037

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3207-7 To add cellular uptake as a release assay for drug product, Brineura (cerliponase alfa), and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.

The timetable you submitted on April 26, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2019

3207-8 To develop and validate an additional identity test method for the Intraventricular Electrolytes Injection [REDACTED] (b) (4)

The timetable you submitted on April 26, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2017

3207-9 To revalidate RP-HPLC and SEC-HPLC release and stability assays using impurities generated by subjecting Brineura (cerliponase alfa) to stressed stability conditions.

The timetable you submitted on April 26, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2017

Submit clinical protocols to your IND 122472 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. 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. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

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 package insert to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

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.

If you have any questions, call Jenny Doan, Regulatory Project Manager, at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

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

/s/

JULIE G BEITZ
04/27/2017