Brineura®
(cerliponase alfa)

COVERAGE AUTHORIZATION GUIDE

BIOMARIN Rare Connections™

Uncommon Support for Rare Disease
1-866-906-6100 or
support@biomarin-rareconnections.com
BioMarin-RareConnections.com

Please see Important Safety Information throughout, and full Prescribing Information.

INDICATION

Brineura® (cerliponase alfa) injection for intraventricular use is indicated to slow the 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.

Contraindications

Brineura is contraindicated in patients with:

- any sign or symptom of acute, unresolved localized infection on or around the device insertion site (e.g., cellulitis or abscess); or suspected or confirmed CNS infection (e.g., cloudy CSF or positive CSF gram stain, or meningitis)
- any acute intraventricular access device-related complications (e.g., leakage, extravasation of fluid, or device failure)
- ventriculoperitoneal shunts

IMPORTANT PREPARATION AND ADMINISTRATION INFORMATION

Brineura must only be administered via the intraventricular route using aseptic technique to reduce the risk of infection. Administer Brineura and the Intraventricular Electrolytes using the provided Administration Kit for use with Brineura components. Prior to each infusion, inspect the scalp for signs of intraventricular access device leakage or failure and for potential infection. Prior to each infusion of Brineura and when clinically indicated, send cerebrospinal fluid (CSF) samples for testing of cell count and culture.

Special Populations

Brineura has not been studied in pregnancy or lactation.

Safety and effectiveness in pediatric patients below 3 years of age have not been established.

WARNINGS AND PRECAUTIONS

Meningitis and Other Intraventricular Access Device-Related Infections

Bacterial meningitis requiring antibiotic treatment and removal of the device was reported during postmarketing use of Brineura. The signs and symptoms of infections may not be readily apparent in patients with CLN2 disease. To reduce the risk of infectious complications, Brineura should be administered by, or under the direction of, a physician experienced in intraventricular administration.

Intraventricular Access Device-Related Complications

During the clinical trial and in postmarketing reports, intraventricular access device-related complications were reported (e.g., device leakage, device failure, extravasation of CSF fluid, or bulging of the scalp around or above the intraventricular access device). In case of intraventricular access device-related complications, discontinue the Brineura infusion and refer to the device manufacturer's labeling for further instructions.

Material degradation of the intraventricular access device reservoir was reported after approximately 4 years of administration, which may impact the effective and safe use of the device. The intraventricular access device should be replaced prior to 4 years of single-puncture administrations, which equates to approximately 105 administrations of Brineura.

Cardiovascular Adverse Reactions

Monitor vital signs before infusion starts, periodically during infusion, and post-infusion in a healthcare setting. Perform electrocardiogram (ECG) monitoring during infusion in patients with a history of bradycardia, conduction disorder, or with structural heart disease. In patients without cardiac abnormalities, regular 12-lead ECG evaluations should be performed every 6 months.

Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in Brineura-treated patients during clinical studies and postmarketing use. In clinical trials, a total of 11 out of 24 patients (46%) experienced hypersensitivity reactions during the infusion or within 24 hours of completion of the infusion.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when Brineura is administered. If a severe hypersensitivity reaction or anaphylaxis occurs, immediately discontinue the infusion and initiate appropriate medical treatment. Observe patients closely during and after the infusion. Inform patients/caregivers of the signs and symptoms of hypersensitivity reactions and anaphylaxis and instruct them to seek immediate medical care should signs and symptoms occur. Consider the risks and benefits of readministration of Brineura following an anaphylactic reaction.

ADVERSE REACTIONS

In clinical trials, the most frequently reported adverse reactions (≥8%) were pyrexia, ECG abnormalities, decreased CSF protein, vomiting, seizures, device-related complications, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension.

Seizures were reported in 12 of 24 patients and included atonic, generalized tonic-clonic, focal, and absence. Seizures were managed with standard anticonvulsive therapies and did not result in discontinuation of Brineura treatment.

Adverse reactions related to the device were observed in 12 of 24 patients. Device-related adverse reactions include infection, delivery system-related complications, and pleocytosis.

Hematoma adverse reactions were reported in 5 patients and presented as hematoma, post-procedural hematoma, traumatic hematoma, and subdural hematoma. Hematomas did not require treatment and did not interfere with Brineura infusion.

Anti-drug antibodies (ADAs) were detected in serum (79%) and CSF (33%) in patients treated with Brineura. No association was found between serum or CSF ADA titers and incidence or severity of hypersensitivity.

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088, or go to www.fda.gov/medwatch.

Please see full Prescribing Information, or visit www.Brineura.com.

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I. Introduction and Disclaimer

Brineura® (cerliponase alfa) injection for intraventricular use is indicated to slow the 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.[1] As an enzyme replacement therapy (ERT), Brineura helps replace the lysosomal enzyme TPP1, which is deficient in individuals with CLN2 disease. The efficacy of Brineura was assessed in a non-randomized single-arm dose escalation clinical study with extension. Brineura-treated patients were compared to untreated patients from a natural history cohort. The Motor domain of a CLN2 Clinical Rating Scale was used to assess disease progression. Over 96 weeks, Brineura helped maintain children's ability to walk, with or without assistance. Brineura was well tolerated, with a favorable safety profile.[1] The most common adverse reactions in patients treated with Brineura include pyrexia, ECG abnormalities including bradycardia, hypersensitivity, decrease or increase in CSF protein, vomiting, seizures, hematoma, headache, irritability, pleocytosis, device-related infection, feeling jittery and hypotension. Brineura is administered via intraventricular infusion every other week.[1]

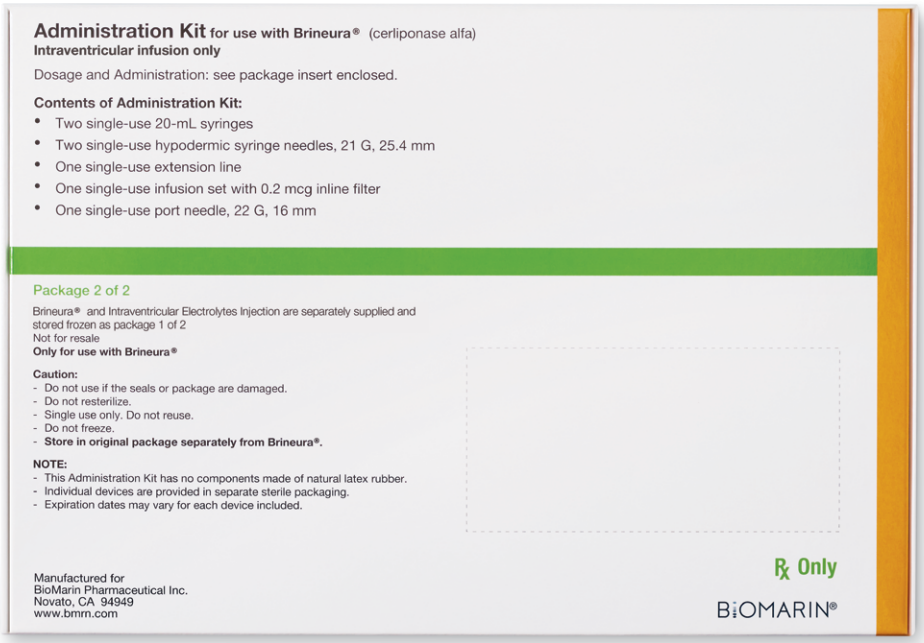
BioMarin, the manufacturer of Brineura, wants to help every patient who is medically appropriate for the product have access to it. Therefore, BioMarin has compiled this guide with information gathered from third-party sources and experienced insurance reimbursement experts to serve as a source of information to assist your institution in obtaining approval and ongoing authorization for Brineura.

BioMarin provides this information as a convenience; it does not constitute legal advice or a recommendation regarding medical practice. Medical coding and billing may vary among payers, and are subject to change without notice because of frequently changing guidelines, laws, rules, and regulations. BioMarin makes no guarantee that the use of this information will prevent denials, delays, or differences of opinion with payers as to the correct form of billing that will expedite payment to providers of service.

Please contact each applicable payer source for counsel when interpreting coding, coverage, and payment policies. This document provides assistance for FDA-approved indications that are documented in the Package Insert (see link below). Where reimbursement is sought for prescribed use and/or administration of this product that may be inconsistent with, or not expressly specified in, the FDA-cleared or -approved labeling outlined in the Package Insert, consult with your billing advisers or payers on handling such issues.

For access-related questions regarding Brineura® (cerliponase alfa) payment or reimbursement, call **1-866-906-6100** or email **support@biomarin-rareconnections.com**.

Please see Important Safety Information throughout, and full Prescribing Information.



Please see Important Safety Information throughout, and full Prescribing Information.

Brineura® (cerliponase alfa)

II. Tips for Insurance Verification for Brineura® (cerliponase alfa)

Patient's benefits should be verified prior to the first dose of Brineura® (cerliponase alfa). Even if the patient has been under the care of your facility for a long time, you may not have gathered all of the information you may need for full coverage of Brineura. This is because different information is often necessary for payment of infused specialty drugs as compared with diagnostic tests, surgery, or an inpatient stay.

The tips below may assist your organization in verifying all benefits that may be necessary to ensure payment throughout the course of Brineura therapy. When you investigate the patient's benefits, these may be necessary for full coverage:

- Ascertain which parent's insurance is primary for the patient in the setting of care where Brineura is administered
- Determine whether a second opinion is required for any aspects of Brineura therapy
- Find the correct organization and its telephone numbers for prior approval or pre-certification (if prior authorization is not required) for drug, surgery, and setting of service care
- Know the plan type (HMO/PPO/other), and determine whether or not your institution is in-network for that specific plan
- Determine whether or not the payer allows rate negotiation for medically necessary and appropriate tertiary care
- Calculate possible deductibles impacting care delivered in the hospital inpatient or outpatient setting, eg, IV drugs, radiology, laboratory tests, chemotherapy administration, or surgery

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II. Tips for Insurance Verification for Brineura® (cerliponase alfa)

- Determine if there is episodic patient cost sharing for care delivered in the inpatient or outpatient setting, eg:
  - Flat copays for drugs; coinsurance payments
  - Coinsurance for surgery (if verifying for it), drugs, drug administration, and/or patient stay
  - Differing patient responsibility by tier for specialty drugs and amount of out-of-pocket costs for the applicable drug tier for Brineura® (cerliponase alfa)
- Determine if the plan has a lifetime, annual, or episodic out-of-pocket maximum
- Determine if the plan has catastrophic coverage (yes/no); if yes, what is the dollar figure where this coverage begins? Calculate the patient's current progress toward qualifying for catastrophic coverage
- Assess whether there are benefit "caps" (limits): lifetime or periodic
- If possible, determine the patient's current status regarding deductibles and out-of-pocket maximums, and current progress toward caps
- Document the specific insurer requirements:
  - Prior authorization/authorization renewal time frame
  - Re-certification of therapy, patient stay, or site of service
  - Case management parameters
  - Appeal guidelines

III. Tips for Prior Authorization

Here are the common health plan forms and documents that may be needed in order to obtain prior authorization.

- **Request for Prior Authorization** (see Section IV) or health plan prior authorization form, if there is one
- Statement of Medical Necessity (see Section V)
- Copy of patient's health plan card
- Supporting documentation:
  - Patient history and physical findings or consultation report(s) discussing the patient's diagnosis and medical necessity for Brineura® (cerliponase alfa) therapy
  - Physicians' chart notes
  - Testing and laboratory results pertinent to a diagnosis of TPP1 deficiency
  - Any hospital admission or emergency room documents/notes
  - Any shared decision-making notes from multidisciplinary discussions or case conferences
  - ICD-10-CM codes pertinent to the diagnosis of TPP1 deficiency, Brineura administration, the placement of the reservoir, and/or secondary diagnoses for the patient. The authorizing body may also request the procedure codes for the reservoir and catheter (intraventricular access device) placement and/or the infusion. Possible codes that may be pertinent to Brineura treatment are in Section VI

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III. Tips for Prior Authorization

Health Plan Guidelines

- Understand each plan's specific guidelines for submitting prior authorization
  - Determine if the plan has a specific website where information can be completed online
  - Check if a specific form is necessary; otherwise, see the **Request for Prior Authorization** in Section IV
- Query if the health plan covers infusion therapies only in a particular setting, such as a doctor's office, an outpatient hospital, or inpatient hospital settings such as NICU, PICU, or regular floor or observation unit

Correct ID Numbers

- It is important to indicate the individual provider ID number versus the group practice/facility provider tax ID number on the Statement of Medical Necessity
- Patient ID number should be taken directly from the patient's health insurance card

Statement of Medical Necessity

- This form may need to be updated and resubmitted, as it is typically valid for only 6 to12 months. *Check with the authorizing entity to ascertain when renewal is required*

Deadlines

- Be sure to know and meet all deadlines for submitting the prior authorization request and other required documents
- Make sure you have clearly documented the date and time that the authorization was received
- Make sure to note the dates for renewal and any other reporting that the plan or utilization management company approving treatment requires

III. Tips for Prior Authorization

Complete Records

- Keep a copy of everything that is submitted to the health plan. Log all calls, and document the date, time, and with whom you spoke in case you need to escalate within the health plan

Out-of-Network/Out-of-State Medical Exception

- Brineura® (cerliponase alfa) is currently offered at a limited number of US institutions, increasing the likelihood that a patient receiving Brineura will seek treatment at a site both geographically located outside of the patient's home state and outside of the patient's in-network, contracted health insurance benefits. As such, prior to administering Brineura, it may be important to obtain an out-of-network medical exception for a patient whose coverage does not have in-network benefits contracted with your institution.

- When seeking an out-of-network medical exception for the patient, it may be useful to (1) emphasize factors unique to the patient case, including whether the healthcare provider(s) place any urgency on access to treatment and (2) describe your healthcare provider(s) and/or institution's expertise with treating Batten disease, and experience or preparedness treating with Brineura.

Site of Service Justification

- There are various settings where Brineura and/or the associated procedures can be administered. It is important to explain in the prior authorization request the intended site of service and the justification for using that site of service for surgery and/or treatment

- In addition, a prior authorization can often be obtained for the product, site of service, and any associated procedure at the same time; conversely, you may find that authorizations for these have to be obtained separately

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IV. An Example Prior Authorization Request

Prior Authorization Request

Date: _____ Time: _____

Contact Person: _____

Telephone Number of Contact Person: _____

Email of Contact Person: _____

Insurance Company Name and Address: _____

Patient's Legal First Name and Last Name*: _____

Date of Birth: _____

Subscriber Name: _____

Subscriber ID Number: _____

Subscriber Group Number: _____

Subscriber Plan Number (if applicable): _____

Effective Date of Coverage: _____

Treating Physician(s): _____

Provider (NPI) Number: _____

Provider Tax ID Number (TIN): _____

*Patient's name must be **exactly** the way it appears on the insurance card.

RE: Authorization for Brineura® (cerliponase alfa)

Dear [Payer Contact],

Please see the enclosed documentation to support the request for prior authorization for my patient [Patient Name], who has been diagnosed with tripeptidyl peptidase 1 (TPP1) deficiency. The patient will be treated with Brineura® (cerliponase alfa) for TPP1 deficiency. On April 27, 2017, the FDA approved Brineura to slow the 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. CLN2 disease is a rare, rapidly progressing neurodegenerative disease. We request the most expedited review of the prior authorization request along with enclosed information. Please provide authorization of surgical placement of the ICV access device necessary for the therapy and for the ongoing intraventricular treatment with Brineura.

IV. An Example Prior Authorization Request

Clinical History

- *Provide brief description of:*
  - *Patient age*
  - *Test results verifying diagnosis*
  - *Functional status*
  - *Treatments to date*
- *Include underlying health issues, symptoms, developmental history, and any disabilities or other factors that impact the treatment decision*
- *Include supporting medical records such as:*
  - *Clinical notes/history and physical/consultation(s), medication records, relevant laboratory reports/results*

Rationale for Brineura® (cerliponase alfa) Therapy

Brineura® (cerliponase alfa) was approved by the FDA on April 27, 2017, and is indicated to slow the 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.

Each infusion consists of 10 mL of Brineura followed by 2 mL of intraventricular electrolytes solution. The intraventricular electrolytes solution is used to fully administer Brineura and to maintain patency of the intraventricular access device.

- *Include benefits of Brineura for the treatment of TPP1 deficiency in this patient*
- *Provide patient's prognosis without treatment*
- *Note site of care and rationale (NICU, PICU, outpatient)*
- *Please see Section VI for potential billing codes for the proposed treatment, if required for prior authorization*

Rationale for Placement of intraventricular access device (ICV device)

Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and intraventricular catheter (intraventricular access device). The intraventricular access device must be implanted prior to the first infusion. The implanted intraventricular access device is for accessing the cerebral ventricles for therapeutic drug administration.

Therefore, if the payer requires codes for approval, please refer to your institution's reservoir placement coding policies, or contact the specified device manufacturer. Section VI of this guide contains some possible codes for the placement of the ICV access device

The recommended reservoirs and catheter below have been tested and are compatible with the provided needle.[2]*

- *Codman®-branded HOLTER RICKHAM reservoirs: part numbers 82-1625, 82-1621, 82-1616*

* These specific reservoirs have been evaluated for administration of Brineura. Other types and brands of reservoirs may not be appropriately cleared for drug administration.

Gauthier-Campbell C, Lester T, Sluzky V. Regulatory challenges of brain delivered therapies: a combination product perspective. *Pharmaceut Reg Affairs.* 2018;7:1-7.

For access-related questions regarding Brineura® (cerliponase alfa) payment or reimbursement, call **1-866-906-6100** or email **support@biomarin-rareconnections.com**.

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IV. An Example Prior Authorization Request

- *Codman®-branded ventricular catheter: part number 82-1650*
- *Note site of care for procedure and rationale (NICU, PICU, outpatient, observation)*

Rationale for Out-of-Network/Out-of-State Medical Exception

- *If your institution requests an out-of-network or out-of-state medical exception, include rationale here.*

Conclusion

My patient [Patient Name] has [patient diagnosis]. [He/She] has been diagnosed with TPP1 deficiency. The patient experienced [history of neurological symptoms and deficits, developmental history]. TPP1 deficiency was affirmatively diagnosed via [include laboratory and genetic testing]. Please review this information for expedited prior authorization of Brineura® (cerliponase alfa) therapy, site of service, and (as appropriate) the placement of the ICV access device.

Thank you for your time and immediate attention to this request.

Sincerely,

[Physician's name, contact information, and credentials]

IV. An Example Prior Authorization Request

Suggested enclosures by HCP:

- FDA approval letter (see Appendix 1)
- Package Insert
- Medical records
  - History and physical or consultation report
  - Laboratory reports verifying the diagnosis

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V. An Example Statement of Medical Necessity

Statement of Medical Necessity

Date: _____

Contact Person: _____

Telephone Number of Contact Person: _____

Email of Contact Person:_____

Insurance Company Name and Address: _____

_____

Patient's Legal First Name and Last Name: _____

Subscriber Name: _____

Relationship to Patient: _____

Subscriber ID Number:_____

Subscriber Group Number: _____

Subscriber Plan Number (if applicable): _____

Effective Date of Coverage:_____

Re: Brineura® (cerliponase alfa) therapy

To Whom It May Concern:

I am writing on behalf of my patient [Patient Name] to request that [Insurance Company Name] approve coverage and appropriate payment for Brineura® (cerliponase alfa) through expedited review. Brineura is a medically necessary treatment for [Patient Name], who has been diagnosed with tripeptidyl peptidase 1 (TPP1) deficiency. This letter provides information about my patient's medical history, diagnosis, and details regarding the appropriateness and medical necessity of the treatment plan with Brineura.

Patient History and Diagnosis

- *Provide brief description of patient's age, functional status, and developmental history*
- *Include laboratory and genetic history verifying the diagnosis*
- *Include underlying health issues, symptoms, and any disabilities or other factors that impact the treatment decision*
- *Include supporting medical records such as:*
  - *Clinical notes/history and physical/consultation(s), medication records, relevant laboratory reports/results*

V. An Example Statement of Medical Necessity

Disease and Treatment Information

Brineura® (cerliponase alfa) injection is FDA approved to slow the 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.

Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device). The intraventricular access device must be implanted prior to the first infusion. The implanted intraventricular access device is for accessing the cerebral ventricles for therapeutic drug administration.

Each infusion consists of 10 mL of Brineura followed by 2 mL of intraventricular electrolytes solution. The intraventricular electrolytes solution is used to fully administer Brineura and to maintain patency of the intraventricular access device. Brineura patients should also be observed by clinicians following therapy.

- *Include benefits of Brineura for the treatment of this particular patient*
- *Provide patient's prognosis without treatment*
- *Note site of care (NICU, PICU, outpatient) for Brineura treatment and surgery for the ICV access device reservoir placement*
- *See example prior authorization request—If your institution requests an out-of-network or out-of-state medical exception, include rationale here.*

We are requesting that you approve treatment with Brineura for this child, [Patient Name]. Should you require additional information, please contact me.

Sincerely,

[Physician's name, contact information, and credentials]

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V. An Example Statement of Medical Necessity

Suggested enclosures:

- FDA approval letter (see Appendix 1)
- Package Insert
- Clinical notes, eg, history and physical, consultation reports
- Relevant laboratory reports

VI. Possible Coding Scenarios for Brineura® (cerliponase alfa) in All Settings

DIAGNOSIS CODES FOR THE DRUG THERAPY INDICATION (USED IN ALL SETTINGS)

DRUG INDICATION	ICD-10-CM CODE 2021	CODE DESCRIPTION
Brineura is a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated for patients with CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.[a]	E75.4	Neuronal Ceroid Lipofuscinosis[a]

[a] While this is not an exact code for TPP1 deficiency, it is the closest descriptor in the ICD-10-CM Tabular List of codes.

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VI. Possible Coding Scenarios for Brineura® (cerliponase alfa) in All Settings

POSSIBLE SECONDARY DIAGNOSIS WHILE PATIENT ON BRINEURA® (CERLIPONASE ALFA) THERAPY

DRUG INDICATION	ICD-10-CM CODE 2021	CODE DESCRIPTION
Medical necessity for drug therapy biweekly for life	Z79.899	Other long-term drug therapy (Z codes represent reasons for encounters. A corresponding procedure code must accompany a Z code if a procedure is performed)

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Brineura® (cerliponase alfa)

VI. Possible Coding Scenarios for Brineura® (cerliponase alfa) in All Settings

POSSIBLE PROCEDURE CODES FOR ICV ACCESS DEVICE PLACEMENT

CODE FAMILY	ICD-10-PCS CODE 2021	CODE DESCRIPTION
Insertion of Infusion Device Into the Brain	00H003Z	Insertion of Infusion Device, Open Approach
	00H033Z	Insertion of Infusion Device, Percutaneous Approach
	00H043Z	Insertion of Infusion Device, Percutaneous Endoscopic Approach
	00H603Z	Insertion of Infusion Device Into Cerebral Ventricle, Open Approach
	00H633Z	Insertion of Infusion Device Into Cerebral Ventricle, Percutaneous Approach
	00H643Z	Insertion of Infusion Device Into Cerebral Ventricle, Percutaneous Endoscopic Approach

Outpatient Procedures

CODE FAMILY	CPT CODE 2021	CODE DESCRIPTION
Implantation of ventricular, catheter, reservoir, or other device	61210	Burr hole(s); for implanting ventricular catheter, reservoir, EEG electrode(s), pressure recording device, or other cerebral monitoring device (separate procedure)
	61215	Insertion of subcutaneous reservoir, pump, or continuous infusion system for connection to ventricular catheter

The following are recommended ICV access device components, which have tested and are compatible with the provided needle: Codman®-branded HOLTER RICKHAM reservoirs: part numbers 82-1625, 82-1621, 82-1616; Codman®-branded ventricular catheter: part number 82-1650

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VI. Possible Coding Scenarios for Brineura® (cerliponase alfa) in All Settings

BIWEEKLY DRUG INFUSION PROCEDURE

Inpatient Procedures

CODE FAMILY	ICD-10-PCS CODE 2021	CODE DESCRIPTION
Introduction of a substance	3E0Q3GC	Introduction of Other Substance Into Cranial Cavity and Brain, Percutaneous Approach
Irrigation and exploration	3E1Q38Z	Irrigation of Cranial Cavity and Brain Using Irrigating Substance, Percutaneous Approach **OR**
Introduction of a substance	3E0Q37Z	Introduction of Other Substance Into Cranial Cavity and Brain, Percutaneous Approach, Electrolytes and Water Balance Substance

VI. Possible Coding Scenarios for Brineura® (cerliponase alfa) in All Settings

OUTPATIENT PROCEDURES AND PROFESSIONAL FEES

There are no definitive codes for a therapeutic infusion of 4 hours and an INTRAVENTRICULAR irrigation in the brain. The codes listed below represent possibilities only. You may choose the one(s) that best matches the documentation in the chart or employ a different code identified in your own research or through discussions with your patient's payer. Please note: The patient may also have charges for outpatient observation room and board, plus professional fee

CODE FAMILY	CPT CODE 2021	CODE DESCRIPTION
Injection, Drainage, or Aspiration Procedures on the Skull, Meninges, and Brain	61026	Ventricular puncture through previous burr hole, fontanelle, suture, or implanted ventricular catheter/ reservoir; with injection of medication or other substance for diagnosis or treatment
Injection, Drainage, or Aspiration Procedures on the Skull, Meninges, and Brain	61070	Puncture of shunt tubing or reservoir for aspiration or injection procedure
Chemotherapy Administration	96542	Chemotherapy injection, subarachnoid or intraventricular via subcutaneous reservoir, single or multiple agents
Chemotherapy Administration	96549	Unlisted chemotherapy administration
Neurology Procedures	64999	Unlisted nervous system procedure
Medicine Procedure	95990	Refilling and maintenance of implantable pump or reservoir for drug delivery, spinal (intrathecal, epidural) or brain (intraventricular), includes electronic analysis of pump, when performed
Medicine Procedure	95991	Refilling and maintenance of implantable pump or reservoir for drug delivery, spinal (intrathecal, epidural) or brain (intraventricular), includes electronic analysis of pump, when performed; requiring skill of a physician or other qualified healthcare professional
Modifiers	-22	Unusual services
Modifiers	-51	Multiple services

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VI. Possible Coding Scenarios for Brineura® (cerliponase alfa) in All Settings

DRUG BILLING FOR BRINEURA® (CERLIPONASE ALFA)

CODE FAMILY	CODE 2021	CODE DESCRIPTION
National Drug Codes (NDC) Please use HIPAA 5-4-2 format[a]	**68135-0811-02 (Carton),**[b] which contains: 68135-0500-00 (2 Brineura® [cerliponase alfa] vials) 68135-0495-04 (Intraventricular Electrolytes vial)	Specific codes to Brineura and to the intraventricular electrolytes infusate
HCPCS Code	J0567	Injection, cerliponase alfa, 1mg
Revenue Codes[c]	0250	Pharmacy: General
Revenue Codes	0258	Pharmacy: IV solutions
Revenue Codes	0261	IV Therapy: Infusion pump
Revenue Codes	0262	IV Therapy: IV therapy/pharmacy services
Revenue Codes	0263	IV Therapy: IV therapy/drug/supply/delivery
Revenue Codes	0636	Pharmacy: Drugs requiring detailed coding

[a] Not all payers require the HIPAA format of 5-4-2 numbers.
[b] The carton National Drug Code most likely will be used for billing.
[c] Revenue codes reference: https://med.noridianmedicare.com/web/jea/topics/claim-submission/revenue-codes.

VII. An Example Appeal Letter for Brineura® (cerliponase alfa)

Appeal Letter

Date: _____

Contact Person: _____

Re: [Patient First Name] [Patient Last Name]

Subscriber Name: _____

Subscriber ID Number: _____

Subscriber Group Number: _____

Subscriber Plan Number (if applicable): _____

Insurance Company Name and Address: _____

_____

Diagnosis and/or Procedure Code(s): _____

Date of Denial: _____

Dear [Name of Contact]:

This letter serves as a formal appeal for the most expedited review of coverage for [Brineura® (cerliponase alfa) and/or the related procedure to place the ICV access device], which was originally denied to [Patient Name] on [Date of Service] for [insert denial reason].

[Patient Name] has been under treatment for [Diagnosis and/or Procedure Code—see Section VI] since [Date of Initial Treatment]. [Insurance Company Name] has stated that [Brineura and/or the procedure for the ICV access device insertion] is not covered because [denial reason].

Treatment Information
On April 27, 2017, the FDA approved Brineura to slow the 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. CLN2 disease is a rapidly progressive neurodegenerative disease, and it's critical that treatment begin for this patient as soon as possible.

Appeal for Brineura and/or the placement of the ICV access device
On [Date], [Patient Name] was infused with 10 mL of Brineura followed by 2 mL of intraventricular electrolytes solution at [insert site of service: eg, PICU, outpatient]. The product was administered at [insert site of care: eg, PICU, inpatient bed, or hospital outpatient]. A catheter was inserted into the [right/left] ventricle of the brain, and a reservoir was accessed to infuse Brineura at 2.5 mL per hour. The infusion takes approximately 4.5 hours. Then a proprietary intraventricular electrolytes solution was used to fully administer all the Brineura solution and to maintain patency of the intraventricular access device.

For access-related questions regarding Brineura® (cerliponase alfa) payment or reimbursement, call **1-866-906-6100** or email **support@biomarin-rareconnections.com**.

Please see Important Safety Information throughout, and full Prescribing Information.

VII. An Example Appeal Letter for Brineura® (cerliponase alfa)

Brineura® (cerliponase alfa) must only be administered via the intraventricular route. It's critical that treatment begin for this patient as soon as possible.

In summary, Brineura was administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device) that was done in the [insert site of care: eg, PICU, outpatient] on [Date]. The intraventricular access device was implanted prior to the first infusion, which was administered on [Date]. The implanted intraventricular access device is necessary to access the cerebral ventricles for therapeutic drug administration.

Patient History and Diagnosis
[Patient Name] is a [Age]-year-old [male/female], who has been under treatment for CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency, since [Date]. Brineura is the only known treatment for this deficiency.

For Denial of Product
[Insurance Company Name] should provide adequate coverage for Brineura because it is medically necessary for CLN2 disease, also known as TPP1 deficiency, and clinically appropriate for this patient, [Name].

- *Insert justification for site of service if applicable*

For Denial of Procedure
[Insurance Company Name] should provide adequate coverage for the procedure to implant the ICV access device because it is medically necessary for the administration of Brineura for TPP1 deficiency. According to its FDA approval, Brineura may only be administered via the intraventricular route. It's critical that treatment begin for this patient as soon as possible.

- *Insert justification for site of service if applicable*
- *Include underlying health issues, symptoms, developmental history, and any disabilities or other factors that impacted the treatment decision*
- *Include supporting medical records such as:*
  - *Clinical notes, medication records, relevant laboratory reports/results*
- *Include site of care justification depending on denial reason*
- *Reference applicable product and procedure codes as needed depending on denial reason. (See Section VI for relevant product and procedure codes)*

On behalf of [Patient Name], we would appreciate your reconsideration of coverage for Brineura and/or the procedure to insert the ICV access device. Please call me at [Primary Treating Site Phone Number] if I can be of further assistance or you require additional information.

Sincerely,

[Treating Provider Name], [Treating Provider Title], [Contact Information], [Provider Number]

VII. An Example Appeal Letter for Brineura® (cerliponase alfa)

Suggested enclosures by HCP:

- Package Insert (see Appendix 1)
- FDA approval letter
- Clinical notes
- Medication records and any relevant laboratory reports

For access-related questions regarding Brineura® (cerliponase alfa) payment or reimbursement, call **1-866-906-6100** or email **support@biomarin-rareconnections.com**.

Please see Important Safety Information throughout, and full Prescribing Information.

APPENDIX 1. Brineura® (cerliponase alfa) FDA Approval Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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 Piramal Pharma Solutions, Inc. in Lexington, Kentucky. 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 ºC. 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 24 months from the date of manufacture when stored at ≤ -60 °C.

Reference ID: 4090146

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)(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 at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see

APPENDIX 1. Brineura® (cerliponase alfa) FDA Approval Letter

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:

APPENDIX 1. Brineura® (cerliponase alfa) FDA Approval Letter

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

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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

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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 [BMN 190 bulk flushing solution (BFS) and BMN 190 flushing solution (FS)].

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:

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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

Please see Important Safety Information throughout, and full Prescribing Information.

Brineura® (cerliponase alfa)

Reference: 1. Brineura® [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; 2020

BIOMARIN®