CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Brineura™

GENERIC NAME
Cerliponase alfa

MANUFACTURER
BioMarin Pharmaceutical Inc.

DATE OF APPROVAL
April 27, 2017

PRODUCT LAUNCH DATE
June 2017

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
Brineura is a hydrolytic lysosomal N-terminal tripeptidyl peptidase 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.

OFF-LABEL USES
Not applicable

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CLINICAL EFFICACY

The safety and efficacy of Brineura was evaluated in an open-label, non-randomized, single-arm dose escalation clinical study. Twenty-four patients, aged 3 to 8 years old were enrolled in the study. One patient withdrew due to challenges with the study procedures. Twenty-three patients received Brineura 300 mg every other week. The primary endpoint was decline in motor domain of the CLN2 clinical rating scale. Decline was defined as having an unreversed 2 category decline or an unreversed score of 0 (normal: 3, clumsy/falls: 2, non-walking: 1, immobile: 0). Evaluation was completed at 48, 72, and 96 weeks.

Motor scores of the 22 Brineura treated patients in the clinical study with extension were compared to scores of the independent natural history cohort that included 42 untreated patients who satisfied inclusion criteria for the clinical study. Of the 22 patients treated with Brineura and evaluated for efficacy at week 96, 21 (95%) did not decline, and only the patient who terminated early was deemed to have a decline. Results from the natural history cohort demonstrated progressive decline in motor function; of the 42 patients in the natural history cohort, 21 (50%) experienced an unreversed (sustained) 2-category decline or unreversed score of 0 in the motor domain of the CLN2 Clinical Rating Scale over 96 weeks.

The results of logistic modeling with covariates (screening age, screening motor score, genotype: 0 key mutations (yes/no)), demonstrated the odds of Brineura-treated patients not having a decline by 96 weeks were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio (95% CI): 13.1 (1.2, 146.9)).

Additionally, at 96 weeks, the matched analysis (22 patients from the Brineura clinical study with a baseline combined motor plus language CLN2 score less than 6 were matched to 42 patients in the natural history cohort) based on 17 pairs demonstrated fewer declines in the motor domain for Brineura treated patients compared to untreated patients in the natural history cohort.

Time Point/Period	**Natural History Cohort (N=17)**	**Brineura-Treated (N=17)**	**Difference**	**Odds Ratio *****
	n (%)	n (%)	% (95% CI **)	OR (95% CI)
Follow-up through Week 48	13 (76)	16 (94)	18% (-19, 51)	4 (0.4, 200)
Follow-up through Week 72	11 (65)	16 (94)	29% (-7, 61)	5.9 (0.7, 250)
Follow-up through Week 96	6 (35)	16 (94)	59% (24, 83)	11 (1.6, 500)

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**Decline is defined as an unreversed (sustained) 2-category decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale.*
*** Exact confidence interval for risk difference (Santner and Snell)*
****Based on McNemar's Exact test*
Matched on baseline age at time of screening within 3 months, genotype (0, 1, or 2 key mutations), and baseline Motor domain CLN2 score at time of screening.
The Brineura-treated population is based on the full population minus two patients with baseline Motor plus Language CLN2 score = 6.

CONTRAINDICATIONS

- Acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection).
- Patients with ventriculoperitoneal shunts.

BLACK BOX WARNINGS

Not applicable

DRUG INTERACTIONS

Not applicable

ADVERSE REACTIONS

Most common adverse reactions (≥8%) are: pyrexia, ECG abnormalities, decreased CSF protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension.

DOSAGE AND ADMINISTRATION

Aseptic technique must be strictly observed during preparation and administration. Brineura should be administered by, or under the direction of a physician knowledgeable in intraventricular administration. Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter.

Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion.

The recommended dosage is 300 mg administered once every other week as an intraventricular infusion followed by infusion of intraventricular electrolytes over approximately 4.5 hours.

PRODUCT AVAILABILITY

Injection: Brineura 150 mg/5 mL (30 mg/mL) solution, two single-dose vials per carton co-packaged with intraventricular electrolytes injection 5 mL in a single-dose vial.

THERAPEUTIC ALTERNATIVES

None available

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Utilization Management Recommendation
• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): i) Opportunity exists to obtain clinically significant medical or laboratory information necessary to determine appropriate use of the medication. (1) Diagnosis should be confirmed with a tripeptidyl peptidase 1 (TPPI) enzyme activity test demonstrating TPP1 deficiency and a TPP1/CLN2 molecular test detecting 2 pathogenic mutations. ii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison
Brineura was not scored because it is the only FDA-approved therapeutic option to slow the loss of ambulation in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2).

References

1. Brineura Prescribing Information. Novato, CA: BioMarin Pharmaceutical Inc.; April 2017. Available at: https://www.brineura.com. Accessed May 2, 2017.
2. Williams RE, Adama HR, Blohm M et al. Management Strategies for CLN2 Disease. Pediatirc Neurology. 2017Apr;(69):102-112. http://dx.doi.org/10.1016/j.pediatrneurol.2017.01.034.
3. Fietz M, AlSayed M, Burke D et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. Molecular Genetics and Metabolism. 2016 Jul;(119):160-167. http://dx.doi.org/10.1016/j.ymgme.2016.07.011.