STUDY SUMMARY

Guidelines on the diagnosis, clinical assessments, treatment and management for neuronal ceroid lipofuscinosis type 2 (CLN2) disease patients

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KEY LEARNINGS FROM THE GUIDELINES[1]

Lack of CLN2 disease awareness may lead to a delayed diagnosis

Effective management and treatment of CLN2 disease requires an early diagnosis

Management of a patient affected by CLN2 disease requires a coordinated, multidisciplinary approach

Supportive and disease-modifying therapies are available to manage CLN2 disease symptoms

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WHAT IS CLN2 DISEASE?[1]

- A rare and rapidly progressing childhood neurodegenerative disorder
- Caused by pathogenic variants in tripeptidyl peptidase 1 (TPP1)
- A heterogenous disease – classical symptomology to a more atypical form
- Early symptoms include new onset seizures, ataxia and language delay, typically between 2–4 years old

WHAT ARE THE GUIDELINES?[1]

- ✓ **21 international experts:** 7 different specialities, including a patient advocate
- ✓ **53 guideline statements** were developed covering 13 domains
- ✓ Comprehensive guidance for the identification and clinical management of patients with CLN2 disease, independent of age and disease severity
- ✓ Lack of symptom awareness can lead to a delayed diagnosis; these guidelines help to address this gap
- ✓ Evidence and consensus-driven guidelines, developed independently of external stakeholder influence
- ✓ Can be used by all HCPs involved in the management of patients with CLN2 disease

CLN2, neuronal ceroid lipofuscinosis type 2; HCP, healthcare professional; TPP1, tripeptidyl peptidase 1.

1. Mole SE, et al. *Orphanet J Rare Dis.* 2021;16:185.

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Study methods and results[1]

EXPERT MAPPING TOOL DEVELOPMENT

An expert mapping tool was developed which ranked multidisciplinary professionals or family support professionals.

- This expert mapping tool could be utilised for other rare disorders

SYSTEMATIC LITERATURE REVIEWS

To develop key statements based on the strength of publications, two systematic reviews were independently and simultaneously conducted.

- Focused on accumulating current evidence for the treatment and management of CLN2 disease
- Results reported in accordance with the PRISMA statement

MODIFIED-DELPHI CONSENSUS

- Clinical care statements were the basis of an international Modified-Delphi consensus determination process
- Statements which reached the consensus mark became the guiding statements
- 53 final recommendations across 13 domains, overall AGREE II assessment score 5.7

RESULTS:

- 41 experts responded to the questionnaire
- Consensus was between 82% and 98%
- 98% of the 53 statements achieved consensus in the first round
- 100% of statements met the consensus benchmarks in the second round

STUDY LIMITATIONS

- The study results represent a point in time
- Further research is required to address current knowledge and evidence gaps, especially the emergence and effect of new treatments
- Not all HCPs responded to all questions
  - They did not all respond as the Steering Committee was multidisciplinary so not all questions were relevant
  - This adds to the strength of the guidelines

AGREE, Appraisal of Guidelines for Research and Evaluation; CLN2, neuronal ceroid lipofuscinosis type 2; HCP, healthcare professional; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

1. Mole SE, et al. *Orphanet J Rare Dis*. 2021;16:185.

Guideline recommendations

1. EARLY DIAGNOSIS[1]

- Effective management and treatment of CLN2 disease requires an early diagnosis (as soon as possible after or before symptom onset)
- Diagnosis is done by biochemical testing following unprovoked seizures and/or unsteadiness in children who may also have a delay/decline in psychomotor development, including speech delay

Patients with the existence of a significant **speech delay** or decline, clumsiness and undiagnosed/unattributed **epilepsy** before the age of 4 should be tested for CLN2 disease.

2. INITIAL EVALUATION USING MULTI-SYSTEM ASSESSMENTS[1]

- Initial evaluation is important to establish a baseline and to monitor disease progression

3. HOLISTIC CARE[1]

- Critical for the patient and their family
- It is recommended that a multidisciplinary team manages the diverse range of disease manifestations

4. TREATMENTS FOR CLN2 DISEASE

BRINEURA®▼(cerliponase alfa) is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.[2]

- Recombinant human TPP1 ERT[2]
- Administered via ICV infusion[1,2]
- Initiation of long-term ERT with cerliponase alfa at 300 mg (or age-appropriate) dose every other week through ICV is recommended[1,2]*
- ERT should be administered by a team experienced in the management of CLN2 disease and required devices[1,2]
- Best practice guidelines for ERT ICV infusion have been published[3,4]

5. PAEDIATRIC PALLIATIVE CARE

Management of CLN2 disease is limited to symptomatic relief and supportive care.[5] These goals and strategies are consistent among experts globally and are guided by the principles of paediatric palliative care, which can be considered under four main themes: quality of life, medical management, end-of-life care and family support.[1,5]

- Common goals in CLN2 disease management go beyond medical management of the patient and extend to supporting the family of the affected child[1,5]
- Care goals evolve over time[1]
- Important considerations for end-of-life care include patient comfort, and support for continued activities and interactions[1]

6. DISEASE MANAGEMENT TOOLS[1]

- Disease-modifying treatment can be considered for any patient diagnosed with CLN2 disease, regardless of phenotype
- Selection of appropriate anti-epileptic drug for seizures
- Supportive therapies: occupational, speech and physiotherapy
- Management of movement disorders, pain and anxiety
- Nutritional care
- Consider child and caregiver vaccination schedule

CLN2, neuronal ceroid lipofuscinosis type 2; ERT, enzyme replacement therapy; ICV, intracerebroventricular; TPP1, tripeptidyl peptidase 1.

***Initiation of long-term ERT is suggested in patients with non-classical TPP1 deficiency after confirmed diagnosis and agreement between parents and provider, as long as no contraindications to therapy exist. Initiation of long-term ERT with cerliponase alfa is recommended in patients with classical CLN2 disease with the potential to benefit from this therapy[1]

1. Mole SE, et al. *Orphanet J Rare Dis*. 2021;16:185. **2.** Brineura Summary of Product Characteristics. **3.** Schwering C, et al. *J Child Neurol*. 2021;36:635–641. **4.** de los Reyes E, et al. *Pediatr Neurol*. 2020;110:64–70. **5.** Williams R, et al. *Pediatr Neurol*. 2017;69:102–112.

Holistic care is key in supporting both patient and family[1,2]

Palliative care framework

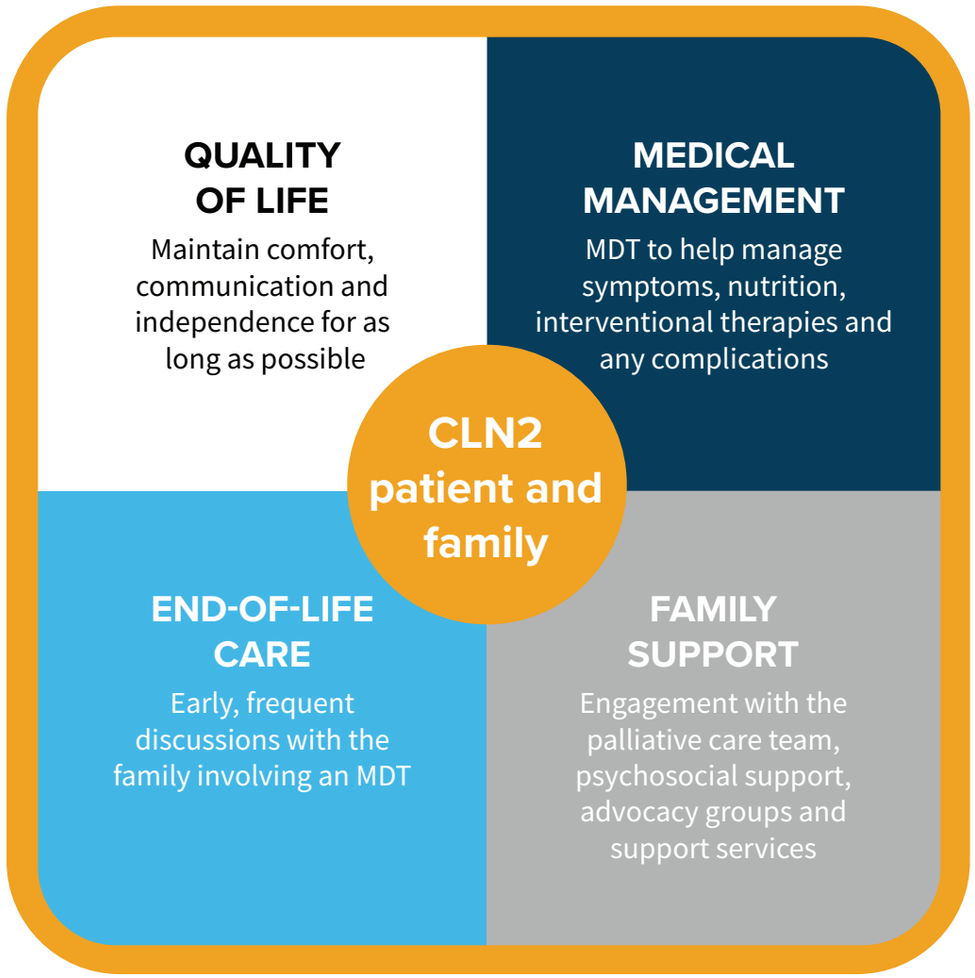
PAEDIATRIC NEUROLOGIST
Rare Disease Specialist to lead patient care

NURSE
To provide ongoing care and support for the patient, as well as being a point-of-contact in the MDT

OCCUPATIONAL & PHYSICAL THERAPIST
To help manage discomfort caused by spasticity

SPEECH THERAPIST
To regularly assess the patient and provide timely provision of supportive devices

MOVEMENT DISORDER EXPERT
To help manage complex movement disorder symptoms



PSYCHOLOGIST
To support the patient and their family with psychological stress associated with the condition

GENETICIST
To provide guidance on the genetics associated with CLN2 disease

DIETICIAN
For guidance on nutrition

SOCIAL WORKER & COUNSELOR
To provide support to the patient and their family

OPHTHALMOLOGIST
To provide baseline assessment and to help manage any ophthalmic degeneration associated with the disease

CLN2, neuronal ceroid lipofuscinosis type 2; MDT, multidisciplinary team.

1. Mole SE, et al. *Orphanet J Rare Dis*. 2021;16:185. **2.** Williams R, et al. *Pediatr Neurol*. 2017;69:102–112.

Abbreviated Prescribing Information: BRINEURA® ▼ (cerliponase alfa)

Abbreviated prescribing information (INTL)
BRINEURA®▼ (cerliponase alfa)
Refer to Summary of Product Characteristics for full prescribing information.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Name of Product: Brineura (cerliponase alfa) 150 mg solution for infusion. **Presentation:** Each vial of Brineura contains 150 mg cerliponase alfa in 5 ml of solution (30 mg/ml). Each presentation contains two vials of cerliponase alfa, and one vial of flushing solution. Cerliponase alfa is a recombinant form of human tripeptidyl peptidase 1 (rhTPP1). **Therapeutic indications:** Brineura is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency. **Dosage and administration:** Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. The recommended dose is 300 mg cerliponase alfa administered once every other week by intracerebroventricular infusion. In patients less than 2 years of age, lower doses are recommended, see full Summary of Product Characteristics. Brineura and the flushing solution must only be administered by the intracerebroventricular route. Each vial of Brineura and flushing solution are intended for single use only. Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intracerebroventricular access device). The intracerebroventricular access device must be implanted prior to the first infusion. The implanted intracerebroventricular access device should be appropriate for accessing the cerebral ventricles for therapeutic administration. **Contraindications:** Life-threatening anaphylactic reaction to the active substance or to any of the excipients, if re-challenge is unsuccessful. CLN2 patients with ventriculo- peritoneal shunts. Brineura must not be administered if there are signs of acute intracerebroventricular access device leakage, device failure, or device-related infection. **Special Warnings and Precautions:** Brineura must be administered using aseptic technique to reduce the risk of infection. Intracerebroventricular access device-related infections, including sub-clinical infections and meningitis, have been observed in patients treated with Brineura. Meningitis may present with the following symptoms: fever, headache, neck stiffness, light sensitivity, nausea, vomiting, and change in mental status. CSF samples should routinely be sent for testing to detect subclinical device infections. In clinical studies, antibiotics were administered, the intracerebroventricular access device was replaced, and Brineura treatment was continued. Healthcare professionals should inspect the scalp for skin integrity to ensure the intracerebroventricular access device is not compromised prior to each infusion. Common signs of device leakage and device failure include swelling, erythema of the scalp, extravasation of fluid, or bulging of the scalp around or above the intracerebroventricular access device. However, these signs may also occur in the context of device-related infections. Inspection of the infusion site and a patency check must be performed to detect intracerebroventricular access device leakage and/or failure prior to initiation of Brineura infusion. The signs and symptoms of device-related infections may not be apparent, therefore, CSF samples should routinely be sent for testing to detect subclinical device infections. Consultation with a neurosurgeon may be needed to confirm the integrity of the device. Brineura treatment should be interrupted in cases of device failure and may require replacement of the access device prior to subsequent infusions. Material degradation of the intracerebroventricular access device reservoir occurs after long periods of use according to preliminary results of benchtop testing and as observed in clinical trials with approximately 4 years of use. In two clinical cases, the ICV access devices did not show signs of failure at the time of infusion; however, after removal, material degradation of the devices were apparent and consistent with data from benchtop testing of ICV access devices. The access devices were replaced and patients resumed treatment with Brineura. Access device replacement should be considered prior to 4 years of regular administration of Brineura, however, it must always be ensured that the intracerebroventricular access device is used in accordance with the provisions of the respective medical device manufacturer. In case of intracerebroventricular access device-related complications, refer to the manufacturer's labelling for further instruction. Caution should be taken in patients prone to complications from intracerebroventricular medicinal product administration, including patients with obstructive hydrocephalus. Anaphylactic reactions have been reported with Brineura. As a precautionary measure, appropriate medical support should be readily available when Brineura is administered. If anaphylactic reactions occur, immediately discontinue the infusion and initiate appropriate treatment. Observe patients closely during and after the infusion. If anaphylaxis occurs, caution should be exercised upon re-administration. **Undesirable Effects:** Very common adverse reactions: Device-related infection, hypersensitivity, irritability, convulsion events, headache, CSF pleocytosis, vomiting, pyrexia, CSF protein increased, ECG abnormalities, CSF protein decreased. Very common product issues: Device leakage, needle issue, device malfunction. Common adverse reactions include: bradycardia, anaphylactic reaction, gastrointestinal disorder, rash, urticaria, feeling jittery, medical device site irritation. Common product issues: Device occlusion and device breakage. Meningitis and device dislocation were also reported at unknown frequency. **List of Excipients:** Sodium phosphate dibasic heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, potassium chloride, magnesium chloride hexahydrate, calcium chloride dihydrate, water for injections. **Incompatibilities:** This medicinal product must not be mixed with other medicinal products. **Storage and Use:** Store upright in a freezer (-25°C to -15°C). Thawed Brineura and flushing solution should be used immediately. Product should only be withdrawn from the unopened vials immediately prior to use to protect from light. If immediate use is not possible, unopened vials of Brineura or flushing solution should be stored at 2–8°C and used within 24 hours. **Preparation of Brineura Infusion:** See full Summary of Product Characteristics. **Legal Category:** Prescription only medicine **Marketing Authorisation Holder:** BioMarin International Limited, Shanbally, Ringaskiddy, County Cork, Ireland. **Marketing Authorisation Number(s):** EU/1/17/1192/001 **Date of First Authorisation:** 30 May 2017 **Date of API revision:** December 2023. Brineura is a trademark of BioMarin Pharmaceutical Inc. from whom further information is available.

Healthcare professionals should report adverse events in accordance with their local requirements.

Adverse events should also be reported to BioMarin on +1 415 506 6179 or drugsafety@bmrn.com

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