



HSE Prescribing Protocol
Cerliponase alfa (Brineura®)
for
Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)

This document is intended for use by healthcare professionals only.

This guideline should be used in conjunction with the full prescribing and administration details in the Cerliponase alfa (Brineura®) Summary of Product Characteristics (SmPC)

https://www.ema.europa.eu/en/documents/product-information/brineura-epar-product-information_en.pdf

INDICATION FOR USE¹

TREATMENT	INDICATION	ICD10	PROTOCOL CODE
Cerliponase alfa (Brineura®)	Treatment of neuronal ceroid lipofuscinosis type 2 (CLN2 or Batten Disease) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency	E75.4	ERT004

This guideline is applicable to both typical and atypical² phenotypes of CLN2 Disease.

TREATMENT¹

TREATMENT	DOSE	ROUTE	FREQUENCY	INFUSION RATE
Cerliponase alfa (Brineura®)	See Table 1 below	Intracerebroventricular infusion	Every two weeks	2.5 mL/hour*

*See cerliponase alfa SmPC for full administration details

Table 1: Dose and volume of cerliponase alfa

AGE GROUPS	TOTAL DOSE ADMINISTERED EVERY OTHER WEEK (mg)	VOLUME OF CERLIPONASE ALFA SOLUTION (ml)
Birth to <6 months	100	3.3
6 months to <1 year	150	5
1 year to <2 years	200 (first 4 doses) 300 (subsequent doses)	6.7 (first 4 doses) 10 (subsequent doses)
2 years and older	300	10

Cerliponase must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.

Pre-treatment of patients with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion¹.

DOSE MODIFICATIONS

See SmPC

ELIGIBILITY CRITERIA

- Patients must have a confirmed diagnosis of CLN2 on the basis of clinical information and enzymatic activity tests. CLN2 diagnosis is made by enzyme (TPP1) and genetic (CLN2 gene) tests on blood samples.

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Protocol Code: ERT004	Approved by: Dr Mike O'Connor National Clinical Advisor & Group Lead, Acute Hospitals	Contributors: Dr D O'Rourke, Prof E Crushell, Dr J Hughes, Prof A Monavari, Prof J O'Byrne, E Losty, H Byrne, F King, R O'Neill	Page 2 of 8
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- The patient has a CLN2 Rating Scale Motor-Language Score of 2 or above (see scoring tool below)
- The patient is not diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g. cancer or multiple sclerosis
- Patients can only start treatment once a full set of baseline criteria has been obtained
- Patient must attend for medical appointments and investigations as determined by the clinical team. The patient is willing to comply with the associated monitoring criteria.
- Patient/carer-clinician discussion prior to commencing treatment regarding the expected outcomes of therapy including the possibility of treatment discontinuation should the disease continue to progress or if the patient is continually non-compliant with monitoring and follow up as defined in this guideline.

In the event of the patient being unable to maintain the above criteria, the implementation of the stop criteria will be discussed with the Patient / Carer.

Table 2: CLN2 Rating Scale Motor-Language Score

CATEGORY	SCORE	DESCRIPTION
Motor	3	Walks normally
	2	Frequent falls, ataxia, independent walk > 10 steps
	1	No unaided gait
	0	Immobile, mostly bedridden
Language	3	Normal
	2	Loss of word, intelligible but abnormal speech
	1	Some comprehension, mostly unintelligible speech
	0	Unintelligible or no speech

EXCLUSION CRITERIA

- Clinically important concurrent disease or co-morbidities which, in the opinion of the specialist team, would not benefit from treatment of the underlying CLN2
- End stage manifestations of CLN2 that mean the patient would be unlikely to benefit from therapy

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
- Cerliponase alfa must not be administered as long as there are signs of acute intracerebroventricular access device leakage, device failure, or device-related infection

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BASELINE TESTS AND MONITORING

Once diagnosed, patients should undergo regular comprehensive assessments to evaluate the outcomes of therapy. Table 3: Recommended schedule of assessments

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ASSESSMENT	BASELINE	3 MONTHLY	6 MONTHLY	12 MONTHLY
Clinical Examination	X	X		
Total CLN2 Disease Rating Scale	X		X	
Weill Cornell Disease Rating Scale	X		X	
Visual Assessment Test	X		X	
ECG, 12 lead	X		X	
EEG, Standard	X		X	
Brain MRI	X			X
FBC, LFT, U&E	X	X		

SPECIAL WARNINGS AND PRECAUTION FOR USE

See SmPC for full details

STOPPING CRITERIA

- A loss of three points or more on the CLN2 Rating Scale ML Score from baseline, during the first eighteen months of treatment and a total CLN2 rating scale score of less than 2;
 - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks)

AND/OR

- During the first eighteen months of treatment, a reduction in proxy reported patient quality of life (when practical to implement) of
 - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference¹); and
 - 0.2² drop in utility as measured by the EQ5D-5L and
 - Decline in CLN2 quality of life assessment of ≥ 15 points

In the case of temporary illness, patients should be retested twice within 12 weeks to ensure that the decline is not as a result of the temporary illness.

1 The accepted minimal clinically important difference (MCID) is 4.5 points for the PedsQL™ [Varni et al. Ambul Pediatr. 2003 Nov-Dec; 3(6):329-41]

2 A minimal clinically important difference of 0.24 based on distribution methods has been estimated. Walters SJ, Brazier JE. Qual Life Res. 2005;14:1523–32.

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Note: The stopping criteria above applies only to those who start treatment at the age of 3 or more. As natural decline in functional endpoints is not evaluable for children under 3, they will be excluded from the stopping criteria until they attain the age of 3. Baseline assessment is the first they receive after reaching the age of 3.

- Continuation of long-term treatment should be subject to regular clinical evaluation whether the benefits are considered to outweigh the potential risks to individual patients
- Patients will cease to qualify for treatment if they miss more than 2 infusions in any 14 month period, excluding medical reasons for missing dosages.
- If a patient is ill prior to an assessment, then the patient needs to be reassessed within 12 weeks and subsequent measures need to be considered from this point
- The patient is diagnosed with an additional progressive life-limiting condition where treatment with cerliponase alfa would not provide long-term benefit.
- The patient develops a life-threatening complication unlikely to benefit from further ERT.
- Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of relevant clinical information to assess their on-going care needs.

ADVERSE EFFECTS

See SmPC for full details

DRUG INTERACTIONS

No formal medicinal product interaction studies have been conducted with cerliponase alfa

ATC CODE

Cerliponase alfa A16AB17

REIMBURSEMENT CATEGORY

CLN2 patients within the public health system will be funded for their treatment with cerliponase alfa by the Health Service Executive (HSE). Prior funding agreement will be sought before initiation of treatment for eligible patients. Once approval for funding has been received (co-ordinated via the Access and Integration Drug Management Programme (AIDMP) aidmp@hse.ie) treatment can be initiated. All new patients and dose increases for existing patients require prior approval via the Enzyme Replacement Therapy (ERT) committee. Funding approval applications can be made and sent to aidmp@hse.ie.

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ADDITIONAL INFORMATION

The enzyme replacement treatment (ERT) outlined in this guideline should be initiated in an appropriate setting for the management of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2 or Batten Disease). A specialist, consultant led, experienced multidisciplinary team who are part of the tertiary treatment centre at CHI at Temple Street or Mater Misericordiae University should lead treatment.

Paediatricians will undertake to refer patients to the adult centre on reaching the age of 16-18 years. Adult and paediatric centres undertake to ensure as much as possible a seamless transfer of care.

Collaboration between the tertiary treatment centres and local primary and secondary care services is imperative to ensuring CLN2 patients receive high standards of care. Local primary and secondary care clinicians will undertake to ensure all CLN2 patients are referred to the specialist team in the tertiary centre for review/ input. They will endeavour to support local colleagues wherever necessary.

Prior to commencing treatment there should be a full discussion regarding the expected outcomes of therapy and the possibility of treatment discontinuation should the disease continue to progress.

REFERENCES

1. Summary of Product Characteristics Brineura® Cerliponase alfa. Available at: https://www.ema.europa.eu/en/documents/product-information/brineura-epar-product-information_en.pdf. Accessed on: 01/04/2025
2. Wibbeler, Dr. E *et al.* Cerliponase Alfa for the Treatment of Atypical Phenotypes of CLN2 Disease: A Retrospective Case Series. *Journal of Child Neurology*. 2021 May;36(6):468-474. doi: 10.1177/0883073820977997.
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4. Canadian Agency for Drugs and Technologies in Health. CADTH Canadian Drug Expert Committee Recommendation: Cerliponase Alfa (Brineura — Biomarin Pharmaceutical [Canada] Inc.) Indication: For the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency. *CADTH Common Drug Review*. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK543392/>. Accessed on 01/04/2025
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APPENDIX

Appendix 1 Weill Cornell LINCL Scale (supplementary disease scoring tool)

FUNCTIONAL CATEGORY	RATING CRITERIA	SCORE
Feeding scale	No swallowing dysfunction	3
	Mild swallowing dysfunction	2
	Moderate swallowing dysfunction	1
	Gastrostomy-tube dependent	0
Gait scale	Normal	3
	Abnormal (spastic or bradykinetic or ataxic) but able to ambulate independently	2
	Abnormal (spastic or bradykinetic or ataxic) requiring assistance	1
	Nonambulatory	0
Motor scale	None of myoclonus, chorea/tremor/athetosis,* and upgoing toes	3
	One of myoclonus or chorea/tremor/athetosis* or upgoing toes	2
	Two of myoclonus or chorea/tremor/athetosis* or upgoing toes	1
	Myoclonus and chorea/tremor/athetosis* and upgoing toes	0
Language scale	Normal speech	3
	Abnormal speech with abnormal articulation or decreased vocabulary	2
	Barely understandable speech with severe dysarthria or very few meaningful words	1
	Unintelligible words or no speech	0
Total score	Feeding score + gait score + motor score + language score	

*Any or more of the three motor symptoms chorea, tremor, and athetosis are considered as one scoring.

LINCL = late infantile neuronal ceroid lipofuscinosis.

Continued Assessment

Patients are required to attend their Metabolic Clinic as clinically indicated. Any additional appointments and clinics must also be attended. It is recognised that some patients for a variety of reasons may not be able to complete all the assessments listed below. All possible efforts should be made to complete as many of the assessments as possible

Appendix 2 Membership of the HSE National Enzyme Replacement Therapy Steering Committee (April 2025)

- Interim Chair: Carol Ivory, Acting Assistant National Director, Specialist Services, Access and Integration
- Fionnuala King, Chief Pharmacist, Access and Integration Drug Management Programme
- Rhona O'Neill, Chief II Pharmacist, Access and Integration Drug Management Programme
- Ita Quinn, Senior Pharmacist, Access and Integration Drug Management Programme

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Representation from Paediatric Centre

- Dr Joanne Hughes, Consultant Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street
- Prof. Ahmad Monavari, Consultant Metabolic Paediatrician, Clinical Director, National Centre for Inherited Metabolic Disorders, CHI at Temple Street
- Dr Caoimhe Howard, Consultant Metabolic Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street
- Dr Ritma Boruah, Consultant Metabolic Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street
- Eithne Losty, Lysosomal Storage Disorders Clinical Nurse Specialist

Representation from Adult Centre

- Prof. James O'Byrne Consultant Physician, National Centre for Inherited Metabolic Disorders, Mater Misericordiae University Hospital, Dublin

Expert advice from

Dr Declan O'Rourke Consultant Neurologist, CHI at Temple Street

HSE National Enzyme Replacement Therapy Steering Committee Position Statement: Patient care for ERT should be led by the centres of excellence with access to a multidisciplinary team with specialist interest in the management of patients with inherited Lysosomal Storage Disorders.

These cerliponase alfa guidelines have been reviewed by a group of prescribing physicians and healthcare professionals working in the treatment centres of excellence in Ireland. The guidelines are designed to standardise practice and support the implementation of treatment pathways for these patients in Ireland.

Appendix 3 Revision History

Revision number	Revision date	Summary of changes
2.0	April 2025	Layout changed to align with other AIDMP Protocols. Removed table of contents. Added table with indication, ICD10 code and protocol code, table with route, frequency and infusion rate. Additional information from SmPC added regarding administration, pre-treatment and continuation.

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