HSE Guidelines for the Treatment of Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) with Cerliponase alfa (Brineura®)

This document is intended for use by healthcare professionals only.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

Cerliponase alfa Guidelines

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.

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Introduction

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 Battens 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.

Diagnosis of CLN2

CLN2 is a rare genetic disease caused by a deficiency of an enzyme called tripeptidyl peptidase 1 (TPP1). A deficiency of TPP1 results in abnormal storage of proteins and lipids in neurons and other cells. Accumulation of these proteins and lipids prevent the cells functioning as they should.

CLN2 diagnosis is made by enzyme (TPP1) and genetic (CLN2 gene) tests on blood samples.

This guideline is applicable to both typical and atypical[1] phenotypes of CLN2 Disease.

Treatment of CLN2

Cerliponase alfa (Brineura®) administered once every other week by intracerebroventricular infusion.

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

(See cerliponase alfa SmPC for full administration details https://www.ema.europa.eu/en/documents/product-information/brineura-epar-product-information_en.pdf)[2]

Eligibility and starting criteria for cerliponase alfa

- Patients must have a confirmed diagnosis of CLN2 on the basis of clinical information and enzymatic activity tests
- 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 / Parent.

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 for cerliponase alfa

- 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

Follow up and monitoring for cerliponase alfa

Once diagnosed, patients should undergo regular comprehensive assessments to evaluate the outcomes of therapy.

Table 4: Recommended schedule of assessments

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		

Stopping criteria for cerliponase alfa

- 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 difference[1]); and

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]

- 0.2^2 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.

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.

- Patients will cease to quality 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.

Additional Information

Audit:

Clinical audit will be undertaken on a biannual basis. This audit will specifically review the patient cohort to ensure that clinical outcome targets (measure of efficacy) as listed in this document are reviewed and

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.

recorded. A recent EMA audit highlighted the need for disease specific registries for outcome evaluation and benefit-risk monitoring of medicinal products. Clinical research, to include outcome analysis and audit, should play a central role in Centres of Expertise. A top–down approach to support research for Centres of Expertise is recommended.

Financial audit will be undertaken in relation to reimbursement of treatment reimbursed centrally. This will specifically monitor the claims made and compliance with eligibility criteria.

Funding of Treatment:

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 Acute Hospitals Drugs Management Programme (AHDMP) ahdmp@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 ahdmp@hse.ie.

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 1.0: 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.

Appendix 2.0 Membership of the Enzyme Replacement Therapy Steering Committee (September 2022)

- Interim Chair: Ms Carol Ivory, Acting Assistant National Director, Acute Operations
- Ms Fionnuala King, Chief Pharmacist, AHDMP.
- Ms Rhona O'Neill, Chief II Pharmacist, AHDMP.

Representation from Paediatric Centre

- Prof Ellen Crushell, Consultant Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- 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.
- Ms 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.

Appendix 3.0 Revision History

Revision number	Revision date	Summary of changes

References:

1. Wibbeler,Dr. E *et al.* Cerliponase Alfa for the Treatment of Atypical Phenotypes of CLN2 Disease: A Retrospective Case Series. *Journal of Child Neurology.* DOI:10.1177/0883073820977997
2. 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: 25/05/2022
3. National Institute for Heatlh and Care Excellence. Cerliponase alda for treating CLN2 Disease. Available at: https://www.nice.org.uk/guidance/hst12/resources/managed-access-agreement-pdf-6968825245. Accessed on: 25/05/2022
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 23/06/2022
5. Australian Government Department of Health. Guidelines for the treatment of late infantile onset Batten disease through the Life Saving Drugs Program The Life Saving Drugs Program. Available online: https://www.health.gov.au/sites/default/files/documents/2020/11/life-saving-drugs-program-batten-disease-guidelines.pdf. Accessed on: 23/06/2022