

Summary of the consideration of the application from BioMarin for the inclusion of Brineura® (cerliponase alfa) on the Life Saving Drugs Program for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease.

Overview:

As an outcome to the Review of the Life Saving Drugs Program (LSDP), the LSDP Expert Panel (LSDPEP) was established to advise the Chief Medical Officer (CMO) on new medicine applications to the program. Cerliponase alfa was the first medicine to be considered under this new process at the Panel's inaugural meeting on 17 August 2018.

Background:

CLN2 disease (also known as late infantile Batten disease) is an ultra-rare, inherited disease caused by pathogenic mutations in the CLN2 gene. Patients with CLN2 disease lack an enzyme called tripeptidyl-peptidase-1 (TPP1) which means that materials accumulate in parts of their nervous system leading to progressive brain damage and a significantly reduced life expectancy.

PBAC Consideration:

At its July 2018 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) considered a submission from BioMarin requesting the listing of cerliponase alfa on the PBS for the treatment of patients with CLN2 disease. The Public Summary Document for the PBAC's consideration of cerliponase alfa states that the PBAC did not recommend the listing of cerliponase alfa "on the basis of unacceptable high cost-effectiveness at the proposed price and uncertainty that the treatment effect observed in the trial would equate to a survival benefit". It also notes that the PBAC considered that the data from the comparison provided in the submission was indicative of a treatment benefit of cerliponase alfa in terms of slowing disease progression.

For further information refer to the Public Summary Document related to the PBAC's consideration: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-07/Cerliponase-psd-july-2018>

Consumer Input:

The LSDPEP noted the consumer input from the PBAC and the LSDP applications. It also heard from stakeholders during the stakeholder presentation at the meeting. The Panel found that the insight provided by the stakeholders was informative and contributed to its deliberations.

LSDP Expert Panel Consideration:

Funding Criteria

In order to be included in the LSDP, a medicine must be considered to meet each of the LSDP funding criteria A1-A8. A summary of the claims for cerliponase alfa against each criterion is presented below.

Criteria		Summary of claims
A1	There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration (TGA).	<p>CLN2 disease is an ultra-rare, inherited disease caused by pathogenic mutations in the CLN2 gene.</p> <p>There have been 35 cases of CLN2 disease in Australia over the period from 2000 to 2016 which corresponds to an incidence of 1 per 135,000 live births; equivalent to 0.74 in 100,000 births.</p> <p>On 28 August 2018, cerliponase alfa was listed on the Australian Register of Therapeutic Goods (ARTG) for “the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency”.</p>
A2	The disease is identifiable with reasonable diagnostic precision.	<p>A diagnosis of CLN2 disease is based on the measurement of a deficiency in TPP1 enzyme activity and/or identification of pathogenic mutations in the CLN2 gene.</p> <p>The TPP1 enzyme and CLN2 gene sequencing diagnostic tests in Australia have been described by Muller et al. (2001).</p> <p>The TPP1 enzyme test and genetic sequencing in Australia is carried out at the National Referral Laboratory, SA Pathology, Adelaide, SA.</p>
A3	Epidemiological and other studies provide acceptable evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease.	<p>The sponsor provided information from the literature to support the claim that the disease causes a significant reduction in age-specific life expectancy. The sponsor reported a median age of death of 10 years.</p>
A4	There is evidence to predict that a patient’s lifespan will be substantially extended as a direct consequence of the use of the drug.	<p>As motor and language functions are the earliest functions to decline in CLN2 disease, a rating scale has been created to determine a patient’s disease progression, known as a Motor-Language score (ML score).</p> <p>The claim against criterion 4 relies on a ML score of zero (MLO) being a proxy for mortality, and treatment with cerliponase alfa delaying progression to MLO.</p> <p>The sponsor stated that:</p> <ul style="list-style-type: none"> the most common causes of death in CLN2 disease are cardiorespiratory failure and sepsis secondary to aspiration pneumonia. Both these conditions occur because of complications from immobility and functional loss (Williams et al., 2017). Immobility and functional loss are represented by MLO which leads to a conclusion that disease-related mortality almost exclusively occurs in patients who have reached MLO. The sponsor reported where ML scores and mortality information are available, most patients (█%) died with MLO. the rate of decline in ML score for patients treated with standard care was estimated to be 2.12 points every 48 weeks, compared to 0.27 points per 48 weeks for patients treated with cerliponase alfa in Study 201/202¹

¹ Schulz, A et al 17 May 2018, ‘Study of Intraventricular Cerliponase Alfa for CLN2 Disease’, *N Engl J Med*, 378 (20):1898-1907. doi: 10.1056/NEJMoa1712649. Epub 2018 Apr 24.

Criteria		Summary of claims
		<ul style="list-style-type: none"> at the most recent data cut (up to 225 weeks) [REDACTED]. <p>In the model presented in the PBAC submission, the application predicted mean survival for patients treated with cerliponase alfa of [REDACTED] years, corresponding to a mean age at death of [REDACTED] years (compared to a mean age at death of approximately 10 years for untreated patients, both in the model presented in the PBAC submission and the literature).</p>
A5	The drug must be accepted as clinically effective but rejected for the PBS listing because it fails to meet the required cost effectiveness criteria.	<p>The PBAC considered that the data from the comparison provided in the submission was indicative of a treatment benefit of cerliponase alfa in terms of slowing disease progression.</p> <p>For further information refer to the Public Summary Document related to the PBAC's consideration: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-07/Cerliponase-psd-july-2018</p>
A6	There is no alternative drug listed on the PBS or available for public hospital in-patients, which can be used as a lifesaving treatment for the disease.	<p>There are no alternative medicines listed on the PBS or available for public hospital inpatients, which can be used as lifesaving treatments for CLN2 disease.</p> <p>The application provided information about the current standard of care for patients with CLN2 disease, noting that management of CLN2 disease is complex and requires a multidisciplinary medical care due to the high symptom load and the rapid rate of functional decline. Specialists typically involved in the management of CLN2 disease include paediatric neurologists, paediatricians, respiratory physicians, ophthalmologists, palliative care specialists, and surgeons.</p>
A7	There is no alternative non-drug therapeutic modality (e.g. surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost effective treatment for this condition.	<p>There are no alternative non-drug therapeutic modalities recognised by medical authorities as suitable or cost effective treatments of CLN2 disease.</p>
A8	The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one year period of the patient, would constitute an unreasonable financial burden on the patient or his/her guardian.	<p>At the proposed price, cerliponase alfa meets this criterion.</p>

Pricing issues

During assessment, it was noted that the proposed cost of cerliponase alfa was high relative to the cost of other LSDP funded enzyme replacement therapies (ERTs).

Overall, it was considered that the price of cerliponase alfa should be no higher than the price of other ERTs of similar effectiveness available on the LSDP for patients in the same age group as the cerliponase alfa treatment cohort. Further, the price should reflect the clinical claim for slowing the progression of the disease rather than halting disease progression.

Note that the price of all LSDP medicines are subject to commercial in confidence arrangements.

Treatment Guidelines

The application included draft Guidelines for the treatment of CLN2 disease through the LSDP, which proposed initial and ongoing eligibility requirements. The Guidelines proposed that:

- All patients with a confirmed diagnosis of CLN2 disease would be eligible to commence treatment, unless they have MLO.
- Provisional eligibility for access to cerliponase alfa would be given based on TPP1 deficiency alone, with genotyping of the CLN2 gene to confirm the diagnosis within 6 months.
- Treatment would continue unless patients have and unreversed MLO or if therapy fails to slow progression of disease.

During assessment, consideration was given to the subjectivity of the ML scores, how transient illnesses can affect the score, the potential difficulty in ceasing perceived life-saving treatment for a child (from funding and clinical perspectives) and that a significant change in the clinical management of a patient should remain in the remit of a treating physician. For these reasons, it was considered that a “stopping rule” would be inadequate to manage this risk. Instead, it was recommended that an appropriate financial cap be negotiated with the sponsor in a Deed of Agreement that will manage any financial uncertainty for the Commonwealth.

Management of Uncertainties

To address uncertainties regarding the clinical effectiveness of cerliponase alfa in terms of the claim of the extent of the survival benefit based on the surrogate outcome of ML score, the application proposed that the ML score should be collected at treatment commencement and at each annual LSDP reapplication for ongoing subsidised treatment. It was recommended that should a patient’s ML score decline by more than two points during the course of treatment, the LSDP is to be notified and is to include a possible explanation (e.g. treatment failure or acute illness).

The application noted that although cerliponase alfa may provide additional benefits in terms of a slowing or stabilisation of vision loss and a reduction in the frequency of seizures, no claim of efficacy is made for these potential improvements. Therefore the application did not propose that data on vision and seizures are collected for the purpose of addressing and

managing uncertainties regarding the (magnitude) of benefit of cerliponase alfa in extending a patient's life expectancy. This was considered reasonable, and it was not recommended that seizure or vision scores be collected.

Context:

The LSDP provides access for eligible patients with rare and life-threatening diseases to essential and very expensive medicines. The LSDP provides eligible patients with access to these life-saving medicines at no expense to the patients or their families.

Before being considered for inclusion on the LSDP, a drug must first be considered by the PBAC and accepted as clinically effective but rejected for PBS listing because it fails to meet the required cost effectiveness criteria.

All applications for new medicines seeking funding through the LSDP are considered by the LSDP Expert Panel. The role of the panel is to provide advice and assistance to the Commonwealth Chief Medical Officer (CMO) on a range of matters relating to new medicines seeking funding, including assessment of how the medicine addresses the LSDP criteria, guidelines for medicine use and testing requirements, suitable pricing arrangements, and data collection required for future reviews.

After receiving advice from the LSDPEP, the CMO advises the Minister for Health on medicines proposed to be included on the LSDP.

This document aims to provide an overview of the evidence considered by the LSDPEP and CMO during their assessment of medicines.

For more information on the process for new medicines seeking funding through the LSDP, refer to the LSDP Procedure guidance:

[http://www.health.gov.au/internet/main/publishing.nsf/content/FD13E541FA14735CCA257BF0001B0AC0/\\$File/Procedure-guidance-for-medicines-funded-through-the-LSDP.pdf](http://www.health.gov.au/internet/main/publishing.nsf/content/FD13E541FA14735CCA257BF0001B0AC0/$File/Procedure-guidance-for-medicines-funded-through-the-LSDP.pdf)

Sponsor's Comment:

BioMarin thanks the LSDP Expert Panel for its review and is pleased that cerliponase alfa is now available for Australian children diagnosed with CLN2.