



**Australian Government**

**Department of Health**

## **Life Saving Drugs Program (LSDP)**

### **24 Month Review Terms of Reference and Protocol Questions:**

Brineura® (cerliponase alfa) for the treatment of  
neuronal ceroid lipofuscinosis type 2 (CLN2)  
disease

## BACKGROUND OF THE REVIEW

The LSDP, administered by the Commonwealth Department of Health, was established in the mid-1990s to provide people with rare and life-threatening diseases access to expensive medicines that were not considered cost-effective for Pharmaceutical Benefits Scheme (PBS) listing. The LSDP currently fully subsidises 16 life-saving high cost medicines for approximately 400 patients for the treatment of 10 rare diseases.

In January 2018, following a review of the LSDP, the Australian Government committed to a number of program improvements, including a review of the medicines currently funded under the LSDP and the establishment of an Expert Panel (EP) to provide advice to the Commonwealth Chief Medical Officer (CMO).

This included the introduction of a mechanism where medicines listed on the LSDP will be subject to a review of usage and financial costs after 24 months, ensuring use and performance of the medicine are in line with the recommendations and expectations at listing and are supported through the Agreement between the Government and Medicines Australia.

Similar reviews will be undertaken on all existing LSDP medicines over the first two years from the commencement of the new program. These reviews will be conducted in accordance with the agreed LSDP [Procedure Guidance](#).

This document describes the Terms of Reference and protocol questions that will guide the 24-month review of cerliponase alfa for the treatment of CLN2 disease.

## PURPOSE OF THE REVIEW

The purpose of 24-month reviews of newly listed medicines on the LSDP is to better understand the real-world use of a medicine by comparing the actual performance and use of the medicine to the recommendations and expectations at the time of listing. The reviews will assess the clinical benefits achieved through the use of LSDP medicines, ensure the ongoing viability of the program, and ensure testing and access requirements for each medicine remain appropriate.

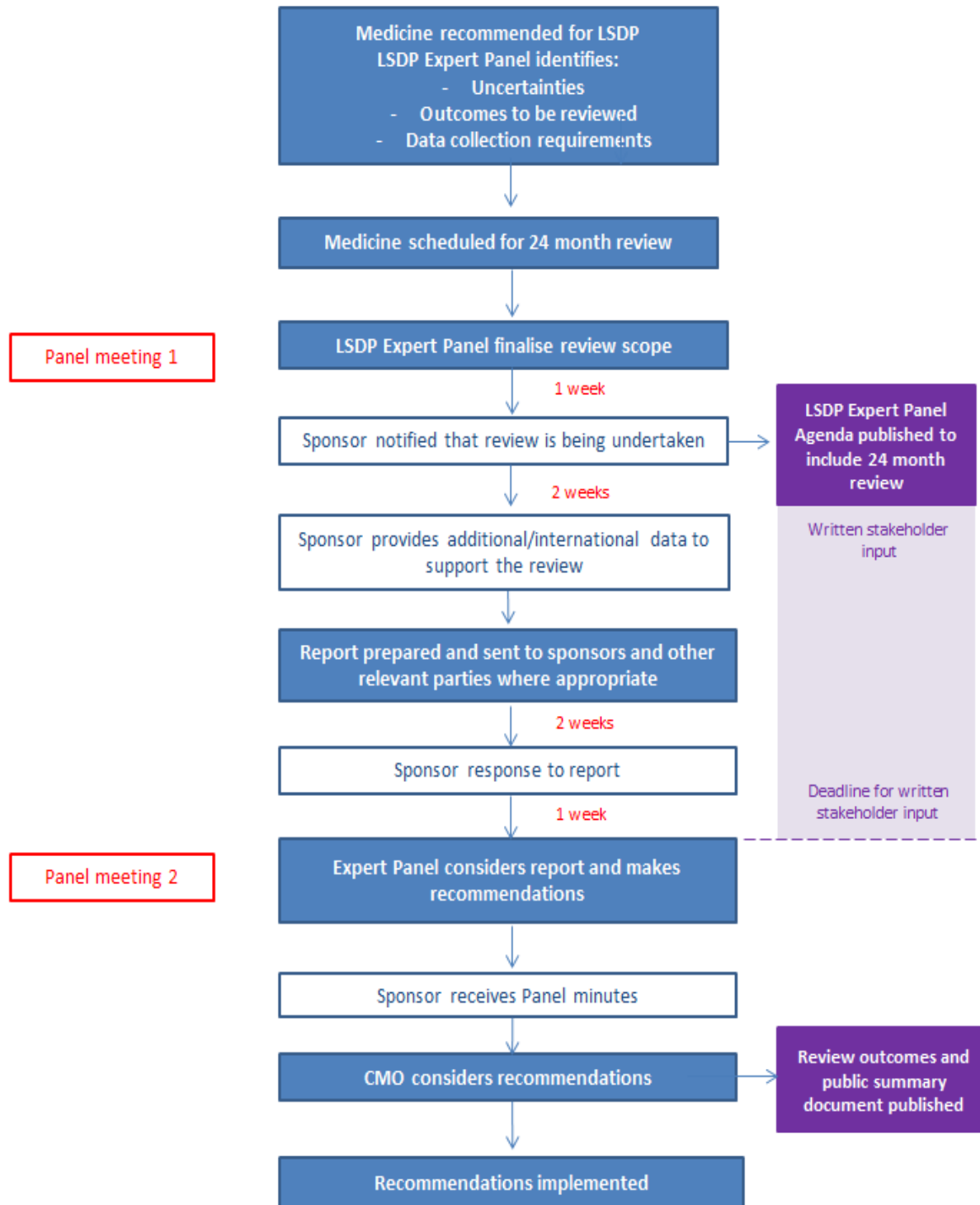
This review evaluates data collected from patients accessing medicines on the program as well as any additional data provided by the sponsor. A report of the findings of the review is completed by the Department. The sponsor of the medicine has an opportunity to consider the report and provide a response. The Expert Panel considers the report, the sponsor response, the key clinician representative response and the key patient representative response when making recommendations.

Where not otherwise specified by the Expert Panel, reviews of new medicines commence 24 months after initial subsidy through the LSDP. The draft scope for the review is established based on issues identified when the medicine was first recommended for inclusion on the LSDP however the scope of the review may be altered by the Expert Panel if new issues have arisen since listing. The figure below outlines the general process for 24-month reviews. More complex reviews or those requiring expert input may take longer.

## NEXT STEPS

Following the review process the Expert Panel will consider the report and make recommendations that align with the Terms of Reference (ToR) and the protocol questions outlined below.

## PROCESS FOR 24 MONTH REVIEWS OF LSDP MEDICINES



## TERMS OF REFERENCE

The ToRs below outline the main aims of this review. Some key protocol questions for consideration are listed below each ToR, noting that the review is not limited to the questions listed and evaluation may provide further advice to the Panel to inform the eventual recommendation(s) for this medicine.

### **ToR 1: Clinical effectiveness and Safety**

This ToR aims to review the available evidence, including evidence collected through the LSDP and outcomes from studies that were still in progress at, or have been performed since, the time of inclusion of cerliponase alfa on the LSDP, to inform judgements regarding the comparative clinical effectiveness and safety of cerliponase alfa. The new evidence should be presented in the context of previous evidence.

#### Protocol Questions

- Are patients who have accessed cerliponase alfa on the LSDP still receiving cerliponase alfa? Have any patient(s) ceased or interrupted treatment with cerliponase alfa and, if so, why is treatment not ongoing?
- What are the most accurate methods for demonstrating efficacy of cerliponase alfa for patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease on the LSDP?
- What are the most appropriate surrogate measures for survival and quality of life?
- What evidence has been generated since the PBAC's prior consideration of cerliponase alfa (from analyses of LSDP patient data or additional data collected by the sponsor or published reports of such analyses) regarding the impact of cerliponase alfa on the rate of progression of disease? Notably, data collection from the sponsor's clinical trial program was continuing at the time of the Panel's recommendation of cerliponase alfa to the CMO and the Panel advised that these data should be reviewed as part of the 24-month review.
- Neurological function:
  - Are the changes in the motor-language (ML) score, as assessed by the CLN2 Clinical Rating Scale, that have been observed in patients treated with cerliponase alfa through the LSDP in line with expectations arising from the data presented at initial submission?
  - To what extent does an ML score of zero correlate with death?
- Survival:
  - What additional evidence has been generated since the sponsor's last submission to PBAC regarding the impact of cerliponase alfa on survival of patients with CLN2 disease?
  - How do the age-adjusted rates of death in patients treated with cerliponase alfa on the LSDP compare with the natural history of CLN2 disease?
- Quality of life:
  - What additional evidence has been generated since the sponsor's last submission to PBAC regarding the impact of cerliponase alfa on quality of life of patients and their carers?

- Other outcomes:
  - Are the outcomes measured in trials and assessed through the LSDP clinically important and/or important to patients/families?
  - Would other measures of efficacy be more useful to clinicians in making ongoing treatment decisions (e.g., change in vision, change in frequency and severity of seizures)?
- Adverse events:
  - Are the number and type of adverse events reported by patients on the LSDP, in post-marketing surveillance studies, and in the literature consistent with expectations arising from the data in the initial study presented to PBAC? In particular, what rates of hypersensitivity reactions, anaphylaxis and infection are being observed?
  - What is the impact of adverse events on patients and their carers, particularly within the context of parents' typical experience of managing their child's symptoms of CLN2?
  - If patient deaths occurred, what is the reported cause of each death (with differentiation of disease-related and treatment-related causes)?

## **ToR 2: Test Validity and Utility**

This ToR aims to review the evidence of the validity and utility of the test to identify patients with CLN2 disease who are candidates for treatment with cerliponase alfa.

### **Protocol Questions**

- Have patients who tested positive for the CLN2 mutation been correctly identified by deficiency of tripeptidyl peptidase 1 (TPP1) in white blood cells, or skin fibroblasts, noting that the LSDP-EP recommended to the CMO that the degree of correlation between TPP1 deficiency and confirmed disease by genotype be reviewed at the 24-month review?
- Has there been a change in disease prevalence? In particular, has there been an increase in diagnosis of CLN2 through increased/improved screening or as a consequence of cerliponase being listed on LSDP)?
- Have new treatments become available since 2019?
- Eligibility:
  - Are the existing eligibility criteria for access to cerliponase alfa on the LSDP fit for purpose?

### **ToR 3: Utilisation and Consumer Impact**

This ToR aims to review the utilisation of cerliponase alfa on the LSDP the impact on consumers.

#### **Protocol Questions**

- Given the existing eligibility criteria, is the appropriate population being treated?
- Is the number of patients receiving treatment with cerliponase alfa on the LSDP consistent with expectations at the time of listing?
- What is the age distribution of patients diagnosed and treated with cerliponase alfa on the LSDP? How many patients are being diagnosed and treated at  $\leq 6$  months,  $\leq 1$  year,  $\leq 2$  years,  $> 2$  years?
- Has the introduction of cerliponase alfa increased the number of CLN2 patients seeking subsidised treatment on the LSDP beyond historical trends prior to availability of cerliponase alfa?
- Consumer impact:
  - Are there outcomes other than ML score, survival and quality of life, that are important to patients and their carers?
  - What (if any) negative impacts do patients experience during treatment with cerliponase alfa (for example out of pocket costs)?

### **ToR 4: Financial Impact**

This ToR aims to review the value for money of cerliponase alfa under the current funding arrangements, including a review of the financial outcomes and future implications of the current listing of cerliponase alfa on the LSDP.

#### **Protocol Questions**

- What are the comparative total (to the program) and average per-patient costs? Have these changed over time? How do they compare with expectations at the time of listing consideration? How do these costs compare with those of other LSDP drugs?
- How do incremental cost-effectiveness ratios (ICERs) for cerliponase alfa in practice compare with ICERs expected at the time of inclusion of cerliponase alfa on the LSDP?
- What is the distribution of doses administered per administration across patients on the program?
- Have the arrangements under the deed of agreement provided adequate management of financial risk?
- To what extent is there wastage of cerliponase alfa (given each administration set contains 2 x 150 mg vials but dose for infants aged up to 6 months is only 100 mg, dose for infants aged 6 months-1 year is 150 mg, dose for those aged 1-2 years is 200 mg only for those aged  $> 2$  years is dose 300 mg)?