



**Australian Government**

**Department of Health**

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

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

Galafold<sup>®</sup> (migalastat) for the treatment of  
Fabry 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 migalastat for the treatment of Fabry 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.

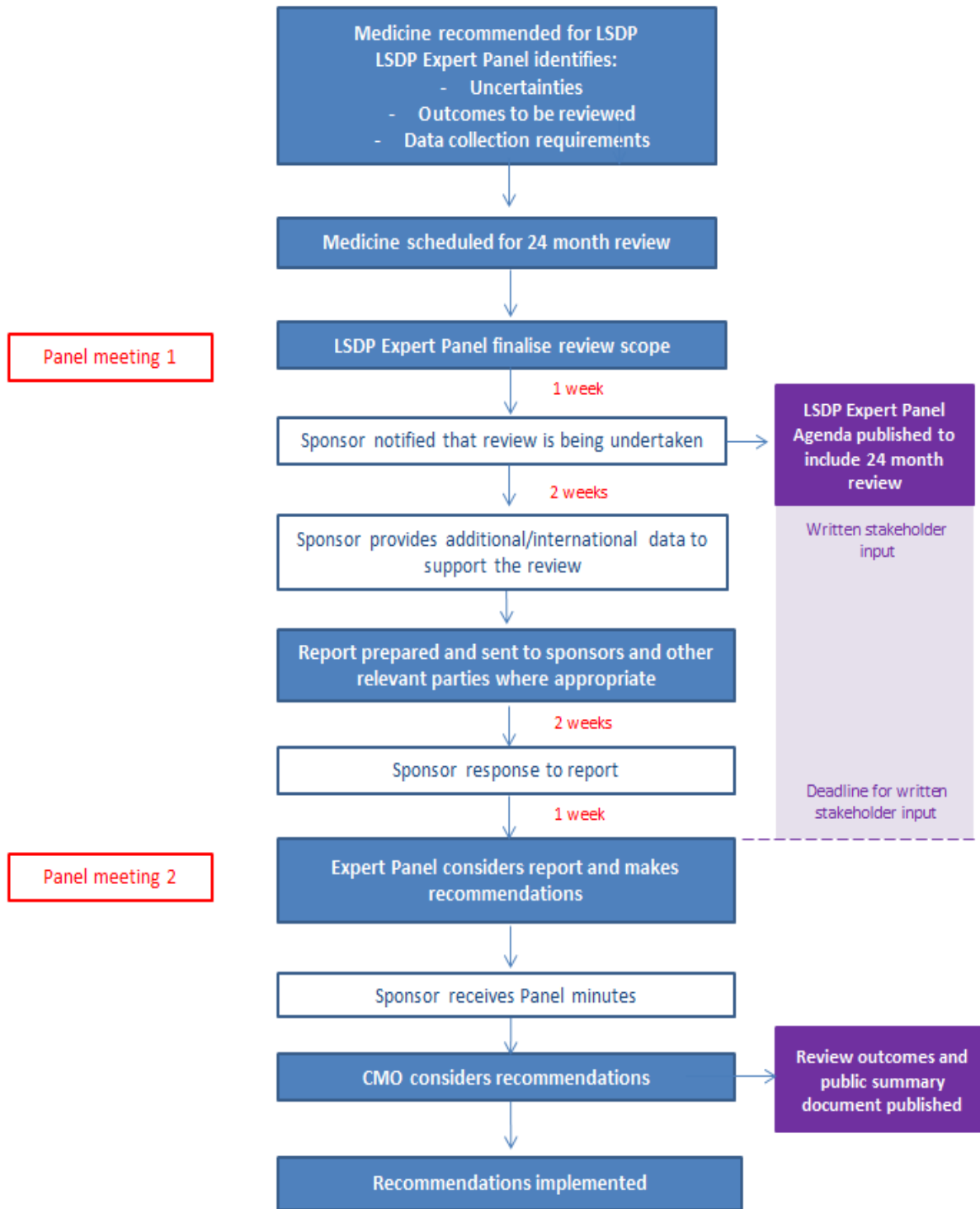
This review evaluates data collected from patients accessing medicines on the program as well as any additional data provided by the sponsor. A report of the findings of the review is completed by the Department. The sponsor of the medicine has an opportunity to consider the report and provide a response. 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 new 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 migalastat on the LSDP, to inform judgements regarding the comparative clinical effectiveness and safety of migalastat. The new evidence should be presented in the context of previous evidence.

#### Protocol Questions

- Are patients who have accessed migalastat on the LSDP still receiving migalastat? Have any patient(s) ceased or interrupted treatment with migalastat and, if so, why is treatment not ongoing?
- What are the most accurate methods for demonstrating efficacy of migalastat for patients with Fabry disease on the LSDP?
- Renal Function
  - What additional evidence has the sponsor collected since its last submission to PBAC regarding the impact of migalastat on renal function?
  - Are the observed changes in glomerular filtration rate (GFR) in patients treated with migalastat through the LSDP in line with the improvements reported in the ATTRACT study?
  - How do GFR results for patients who have been treated with migalastat through the LSDP compare with the results for the same patients while they were previously on ERT?
  - Is there evidence of deterioration or improvement in GFR on migalastat?
- Cardiac Function
  - What additional evidence has the sponsor collected since its last submission to PBAC regarding the impact of migalastat on cardiac function?
  - How do left ventricular (LV) mass results for patients who have been treated with migalastat through the LSDP compare with the results for the same patients while they were previously on ERT?
  - Is there evidence of deterioration or improvement in LV mass on migalastat?
- Survival
  - What evidence has been generated since the PBAC's prior consideration of migalastat (from analyses of LSDP patient data or additional data collected by the sponsor or published reports of such analyses) regarding the impact of migalastat on the rate of progression of disease?

- Quality of life
  - What additional evidence has been generated since the sponsor's last submission to PBAC regarding the impact of migalastat on quality of life of patients and their carers compared with ERT?
- What are the most appropriate surrogate measures for survival and quality of life?
- 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?
- 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? Are they in line with the results from the ATTRACT study? In particular, what rates of hypersensitivity reactions, anaphylaxis and infection are being observed?
  - How does the incidence of adverse events in patients treated with migalastat through the LSDP compare with the incidence of adverse events in the same patients while they were previously on ERT? If switching was for intolerance, has that issue recurred or persisted or resolved?
  - What is the impact of adverse events on patients and if applicable, their carers, particularly within the context of patients' typical experience of managing their symptoms of Fabry disease?
  - 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 Fabry disease who are candidates for treatment with migalastat.

### Protocol Questions

- Have patients who tested positive for the amenable mutation been correctly identified by the GLA-HEK assay?
- Has the GLA-HEK assay appropriately identified patients who will derive a benefit from migalastat?
- Has there been a change in disease prevalence? In particular, has there been an increase in diagnosis of Fabry disease through increased/improved screening or as a consequence of migalastat being listed on LSDP)?
- Have new treatments become available since 2019?
- Eligibility:
  - Are the existing eligibility criteria for access to migalastat on the LSDP fit for purpose?

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

This ToR aims to review the utilisation of migalastat on the LSDP and the impact on consumers.

#### Protocol Questions

- Given the existing eligibility criteria, is the appropriate population being treated?
- Is there an association between the introduction of migalastat and the number of Fabry patients seeking subsidised treatment on the LSDP beyond historical trends prior to availability of migalastat?
- Are new migalastat patients on the program primarily as a result of switching from other LSDP-subsidised ERT at the request of treating clinicians (noting that the ATTRACT trial population was limited to patients switching from ERT)?
  - Is switching due to intolerance or patient preference?
  - What is the key intolerance?
  - What is the average time to, and what is the distribution around the average time to, switch to migalastat relative to commencement of any LSDP treatment?
- Consumer impact:
  - What, if any, changes in patient-relevant outcomes have been reported due to the oral route of administration with migalastat compared to IV route of administration with ERTs? Are there any other outcomes that are important to patients and their carers?
  - What (if any) negative impacts do patients experience during treatment with migalastat compared to those treated with ERT (for example out of pocket costs)?
  - What, if any, other changes in patient-relevant outcomes have been reported by patients treated with migalastat compared with ERT?

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

This ToR aims to review the value for money of migalastat under the current funding arrangements, including a review of the financial outcomes and future implications of the current listing of migalastat 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 migalastat in practice compare with ICERs expected at the time of inclusion of its inclusion on the LSDP? Has the oral formulation reduced the other indirect costs (for example, patient or public health) of treating Fabry disease with LSDP drugs?
- Have the arrangements under the deed of agreement provided adequate management of financial risk?
- The sponsor claimed that the fixed-dose formulation of migalastat would lead to savings over the weight-based ERT formulations. Has this eventuated?