Australian Government

Department of Health and Aged Care

Life Saving Drugs Program (LSDP)

24 Month Review Terms of Reference and Protocol Questions:

Vimizim® (elosulfase alfa) for the treatment of Mucopolysaccharidosis Type IVA (Morquio A Syndrome)

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 24month-like review of elosulfase alfa for the treatment of Mucopolysaccharidosis Type IVA (MPSIVA).

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 process for a 24 month review involves the preparation of a review report, for consideration by the Panel. Sponsors are asked to provide input into the review and to consider the report before the final version is presented to the Panel for its consideration. Stakeholders can provide written input into the review and for consideration by the Panel. Due to the complex nature of this review, the Expert Panel has approved a longer review timeframe, to take place over two Panel meetings.

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.

Elosulfase alfa (Vimizim®) for the treatment of Mucopolysaccharidosis Type IVA (Morquio A Syndrome)

TERMS OF REFERENCE

The Terms of Reference (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 the 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 elosulfase alfa for Mucopolysaccharidosis Type IVA (MPS IVA) on the LSDP, to inform judgements regarding the comparative clinical effectiveness and safety of elosulfase alfa. The new evidence should be presented in the context of previous evidence considered by the PBAC and the EP.

Protocol questions:

- Are patients who have accessed elosulfase alfa on the LSDP still receiving elosulfase alfa? Have any patient(s) ceased or interrupted treatment with elosulfase alfa and, if so, why is treatment not ongoing? Due to the small patient numbers, analyses will need to consider how each individual patient has responded to treatment, with this longitudinal analysis to provide a more holistic approach.
- What are the most accurate methods for demonstrating efficacy of elosulfase alfa for patients with MPS IVA on the LSDP? Are the four clinical parameters [redacted] the most appropriate (6 minute walk test (6MWT), forced vital capacity (FVC), urinary keratan sulfate (uKS) and ejection fraction (EF))?
- Are the changes in the functions, as assessed by the MPS IVA measures (6MWT, FVC, uKS and EF), that have been observed in patients treated with elosulfase alfa through the LSDP, in line with expectations arising from the data presented at initial submission?
- 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 elosulfase alfa (from analyses of LSDP patient data or additional data collected by the sponsor, or published reports of such analyses) regarding the impact of elosulfase alfa on the rate of progression of disease? [redacted]
- Quality of life:
    - What additional evidence has been generated since the sponsor's submission to PBAC regarding the impact of elosulfase 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?
    - Are other measures of efficacy 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, observed in post-marketing surveillance studies and reported in the literature, consistent with expectations arising from the data in the initial study/studies presented to PBAC? In particular, what rates of hypersensitivity reactions, anaphylaxis and infection are being observed in practice? Has anyone been removed from the LSDP due to adverse events?
    - What is the impact of adverse events on patients and their carers?
- A recommendation from some of the Reviews of existing LSDP medicines was that the exclusion criterion included for all LSDP drugs regarding patients enrolled in clinical trials must cease treatment with their LSDP subsidised drug be removed. Would a similar change be appropriate for elosulfase alfa?

ToR 2: Test Validity and Utility

This ToR aims to review the evidence of the validity and utility of the tests to identify patients with MPS IVA who are candidates for treatment with elosulfase alfa.

Protocol questions:

- An overarching recommendation from the Reviews of existing LSDP medicines was the acknowledgment of the importance of analytical validity, clinical validity, and clinical utility when considering the value of health technologies, particularly for initial and ongoing eligibility requirements. The purpose, clinical benefits and frequency of undertaking additional specific clinical monitoring tests for initial and ongoing subsidy compared with routine clinical care needs to be clarified.
    - Treating physicians are best placed to provide input on any discordance between the tests required for initial ongoing eligibility, and that which are used in routine clinical practice, and a formal HTA (Health Technology Assessment) should be conducted for any tests that are required solely for eligibility purposes.
    - At the time of listing, the PBAC noted that the ongoing eligibility criteria for the 6MWT and forced vital capacity might not be appropriate as they were based on the mean change in untreated patients. Does the evidence suggest these tests do not have the appropriate utility for the LSDP?
    - Are the existing eligibility criteria fit for purpose?
- Have patients who tested positive for the mutations in the GALNS gene been correctly identified and results supported by 6 month review point testing of elevated urinary keratan sulfate (uKS) and deficiency of N-acetylgalactosamine-6-sulfatase (GALNS) in white blood cells or skin fibroblasts, noting that not all individuals with MPS IVA will have 2 pathogenic mutations?
- The 6MWT and FVC are not required for patients under 5 years of age. What proportion of the LSDP population are in this age group, and are there any equivalent or alternative tests available?
- Has there been a change in disease prevalence? In particular, has there been an increase in diagnosis of MPS IVA through increased/improved screening or as a consequence of elosulfase alfa being listed on LSDP?
- Have any new treatments become available since 2017?

ToR 3: Utilisation and Consumer Impact

This ToR aims to review the utilisation of elosulfase alfa on the LSDP and its impact on consumers.

Protocol questions:

- Given the existing eligibility criteria, is the appropriate population being treated?
- Is the number of patients receiving treatment with elosulfase alfa on the LSDP consistent with expectations at the time of listing?
- What is the age distribution of patients diagnosed and treated with elosulfase alfa on the LSDP?
- Has the introduction of elosulfase alfa increased the number of MPS IVA patients seeking subsidised treatment on the LSDP beyond historical trends prior to availability of elosulfase alfa?
- Is the exclusion criterion for patients who miss more than 3 infusions in any 14 month period (excluding medical reasons) suitable, noting elosulfase alfa is the only LSDP drug that has this requirement?
- Consumer impact:
    - Are there outcomes other than endurance, respiratory function, uKS and cardiovascular function that are important to patients and their carers?
    - What (if any) negative impacts do patients experience during treatment with elosulfase alfa (for example out of pocket costs)?

ToR 4: Financial Impact

This ToR aims to review the value for money of elosulfase alfa under the current funding arrangements, [redacted] and future implications of the current listing of elosulfase alfa on the LSDP.