Australian Government
Department of Health and Aged Care

Life Saving Drugs Program (LSDP): Review of Medicines for Mucopolysaccharidosis Type I (MPS I)

Review summary and expert panel recommendations

Purpose of the MPS I Review

Laronidase (Aldurazyme®) was listed on the LSDP for MPS I on 1 August 2007. The Expert Panel considered this review at its October 2020 meeting and out of session.

This review of laronidase sought to develop a better understanding of this LSDP medicine by comparing its current use against the recommendations and expectations at the time of listing.

The review further aimed to assess the clinical benefits achieved through the use of laronidase; ensure the ongoing viability of the LSDP; and ensure testing and access requirements for laronidase remain appropriate. It identified immediate and future changes that may be required to the funding criteria for laronidase and to the LSDP more broadly.

The review of each of the LSDP medicines was supported by an approved disease specific Review Protocol, which was structured around seven Terms of Reference (ToRs). The ToRs were tailored specifically to each disease and the relevant medicine(s).

MPS I Medicine Review Terms of Reference

1. Review the prevalence of MPS I in Australia.
2. Review evidence for the management of MPS I and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of laronidase on the program (including the validity of the tests).
3. Review clinical effectiveness and safety of laronidase for the treatment of MPS I, including analysis of LSDP patient data and international literature to provide evidence of life extension.
4. Review relevant patient-based outcomes that are most important or clinically relevant to patients with MPS I.
5. Assess the value for money of laronidase under the current funding arrangements by evaluating the benefit of its treatment outcomes and cost.
6. Review the utilisation of laronidase including storage, dispensing and evidence of patient compliance to treatment.
7. Investigate developing technologies that may impact future funded access.

Key Findings and Recommendations from the Expert Panel

ToR 1 – Review the prevalence of MPS I within Australia

The Expert Panel noted the prevalence of MPS I, as estimated in the Report, is 1.15 per 100,000 births (which is similar to the prevalence estimated at the time of listing). This is less than the 1:50,000 threshold for a rare disease on the LSDP.

Recommendation 1:

The Expert Panel considered that MPS I meets the prevalence criterion of less than 1:50,000 and on that criterion currently remains suitable for inclusion on the LSDP.

The Expert Panel advised that the prevalence of MPS I be reviewed five years post implementation of Government agreed changes to determine whether it continues to meet the definition of a rare disease.

ToR 2 – Review evidence for the management of MPS I and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of laronidase on the program (including the validity of the tests)

The Expert Panel noted the LSDP eligibility criteria for access to subsidised laronidase for MPS I are more restrictive than those applying internationally, particularly for use in:

- combination with stem cell transplant
- patients with mild disease
- presymptomatic disease; or
- severe forms of the disease including low cognitive function.

Stakeholders were supportive of broadening the eligibility criteria to include these patients. The Expert Panel noted laronidase use in these patients has not been assessed for subsidy purposes on the LSDP.

The Expert Panel noted the LSDP requirements for testing were more frequent than recommended in published guidelines and this was having an impact on patients. The LSDP data indicated most of these tests were not being conducted by treating physicians on a regular basis.

Recommendation 2:

The Expert Panel recognised that the current LSDP patient eligibility treatment criteria are narrower than current expert opinion. Accordingly, the Expert Panel recommended that sponsors submit applications for the Expert Panel's consideration in support of amending/revising the eligibility criteria for commencement and continued access to treatment for MPS I. Submissions must include an assessment of the clinical, economic and financial implications if expanded access is a likely consequence of adoption of any proposal by the sponsor.

Recommendation 3:

The Expert Panel acknowledged the importance of analytical validity, clinical validity, and clinical utility when considering the value of health technologies, particularly in this context for the purpose initial and ongoing eligibility requirements. The Expert Panel agreed that 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 and ongoing eligibility, and that which are used in routine clinical practice, and a formal health technology assessment should be conducted for any tests that are required solely for eligibility purposes. The Expert Panel recommended that further clinical advice be sought for review of the following ongoing clinical tests:

- Imaging requirements
- Cognitive testing
- Ophthalmological assessments
- Sleep studies
- Functional tests.

ToR 3 – Review clinical effectiveness and safety of laronidase for the treatment of MPS I, including analysis of LSDP patient data and international literature to provide evidence of life extension

The Expert Panel noted the Pharmaceutical Benefits Advisory Committee (PBAC) had previously concluded the evidence presented in the clinical trial ALID 003-99 was insufficient to support either a clear efficacy difference or a clear toxicity difference between laronidase and placebo.

The Expert Panel also noted the two extension studies presented in the Review that were not available at the time of PBAC consideration. While one study did not provide comparative evidence on the impact of laronidase on survival outcomes in patients with MPS I, it showed the use of enzyme replacement therapy (ERT) results in survival outcomes that are beyond those observed historically in MPS I patients. The results of the second study suggest initiation with ERT may prevent and minimise irreversible damage.

An additional study indicated laronidase has a positive impact on patients' improvement in quality of life (QoL).

The Expert Panel noted the limitations of the LSDP dataset; however, the survival benefit observed in LSDP patients appears to be less than that reported in publicly available literature. The Expert Panel discussed that due to the natural course of MPS I, and in the absence of treatment with laronidase, patient clinical outcomes are likely to be poor. Maintenance or slowing of deterioration (as opposed to an improvement) over time is an outcome providing benefit for patients and their families (and is valued by treating physicians).

Recommendation 4:

The Expert Panel noted the limitations of the available evidence regarding the conclusion that laronidase extends survival for MPS I patients. The Expert Panel noted that maintenance or slowing of deterioration in clinical outcomes through the use of laronidase is an important outcome. Therefore, on the basis of the evidence identified through the Review, the Expert Panel advises that laronidase remains suitable for inclusion on the LSDP.

Recommendation 5:

The Expert Panel noted that data available to estimate the survival benefit observed in LSDP patients treated with laronidase is limited, although there is evidence demonstrating a delay in deterioration. Some patients experience a decline in percent predicted forced vital capacity (ppFVC), although considerable uncertainty about the impact on survival exists. The Expert Panel advised that a price reduction be negotiated with the sponsor on this basis.

ToR 4 – Review relevant patient based outcomes that are most important or clinically relevant to patients with MPS I

The Expert Panel noted the treatment outcomes that are most important to patients and their families as found in the Review. These included improvement in symptoms, general functioning and QoL. These were evidence of stabilisation of disease and improvement of musculoskeletal symptoms. Treating physicians noted this resulted in the reduced need for mobility and other aids.

The sponsor considered the improvements observed in the most relevant functional outcomes for patients and carers aligned with the clinical trial outcomes.

The Expert Panel noted stakeholder feedback around the burden of the testing requirements, also discussed in ToR 2.

Recommendation 6:

The availability of consistent and complete data extracted from initial and ongoing applications to the program is essential, particularly that related to patient outcomes. Consistent with recommendation 3 in relation to ToR 2, the Expert Panel recommended that:

(i) The instrument used to measure pain and QoL be reviewed

(ii) The extent and methods of data collection be revised

(iii) The approach to analysis of the data be improved.

The LSDP should implement a streamlined solution that enables treating physicians to enter patient data both for everyday administration of the program and for future medicine reviews. The Expert Panel recommended that this revised approach should improve clinical and patient satisfaction and facilitate availability of complete and comprehensive data for any future review of MPS I medicines.

ToR 5 – Conduct an analysis of the value for money of laronidase under the current funding arrangements by evaluating the benefit of its treatment outcomes and cost

The Expert Panel noted the estimated Incremental Cost Effectiveness Ratio (ICER) was $[redacted] per improvement in ppFVC (i.e. respiratory function outcomes) and $[redacted] per 11 percent improvement in predicted FVC. These ratios were lower than the results in the 2004 PBAC submission, which presented ICERs of $[redacted] per improvement in ppFVC and $[redacted] per 11 percent improvement in predicted FVC. However, the lower values are mainly due to changes in the cost of laronidase and health services.

The Expert Panel noted the estimated ICER of $[redacted] per additional patient achieving a clinically meaningful improvement (gain of 54 metres) in the six-minute walk test (6MWT) with laronidase compared with standard medical management. An estimated cost per life year gained (based on data from a retrospective multi-centre cohort study comparing long term survival in patients treated with ERT, haemopoietic stem cell transplant, and no treatment) was approximately $[redacted], although this was difficult to determine due to limited data availability.

The Expert Panel considered that, while the Review found the clinical data did not provide evidence of life extension, the improvement in QoL outcomes in MPS I patients treated with laronidase was indicative of clinical benefit from treatment.

Recommendation 7:

The Expert Panel noted that there appears to be a survival gain and improvement in QoL from treatment with laronidase, and that the cost of this medicine remains very high. Due to uncertainty of survival gains as a result of limited data, costs associated with laronidase treatment may be even higher than current estimates. The Expert Panel therefore recommended that the pricing and listing arrangements for laronidase be reassessed with the goal of improving value for money when:

(i) current deeds of agreements with sponsors expire; and/or

(ii) new medicines for MPS I are considered for entry onto the LSDP or other subsidy programs; and/or

(iii) changes in eligibility criteria are being considered.

ToR 6 – Review the utilisation of laronidase, including the way it is stored and dispensed, and evidence of patient compliance to treatment

The Expert Panel noted the estimated average prescribed and dispensed doses (0.60 mg/kg/week and 0.65 mg/kg/week respectively) per patient were higher than recommended in the Product Information for laronidase (0.58 mg/kg). Feedback from stakeholders noted dosages were rounded up to the nearest full vial. The Expert Panel recommended the sponsor be requested to either make a smaller vial available or to adjust pricing of the single vial to account for use of the medicines in excess of the weight-based dose approved in the Product Information.

MPS I patients appeared to be compliant with laronidase treatment.

The Expert Panel noted there were reported low levels of laronidase administration in the home setting which is not explicitly allowed in the Product Information. One treating physician requested a home infusion program be introduced to alleviate some of the burden on patients and carers. The Expert Panel was supportive of this but noted establishment of such a program was outside the remit of the LSDP.

The Expert Panel considered the value for money aspects of a weight based dosing and funding approach should be reassessed. In particular, the Commonwealth should only be reimbursing for the dose of drug prescribed by the treating physician within the approved Product Information doses.

Recommendation 8:

The Expert Panel advised that should the Product Information be formally updated to allow for home infusions of laronidase, the Expert Panel and LSDP would be in support of amending the MPS I LSDP Guidelines to include this service to potentially improve care for patients.

ToR 7 – Investigate developing technologies that may impact future funded access

The Expert Panel noted the introduction of gene-based therapies, substrate reduction therapies, and improvements in the delivery of ERT and in the approach to stem cell transplant will likely have an impact on MPS I and laronidase use. Of note were the results of the gene-based therapy trials which were expected to be available within the next two to three years.

The Expert Panel discussed the impacts of the exclusion criterion for patients being treated with LSDP laronidase and wishing to participate in a clinical trial. This is a non-disease specific criterion across all LSDP disease Guidelines.

The Expert Panel noted newborn screening may lead to a high number of false positives for patients with milder presentations of MPS I who would not be eligible for subsidised laronidase treatment.

Recommendation 9:

The Expert Panel recommended that the exclusion criterion that prevents patients being treated with LSDP funded medicines whilst participating in clinical trials should be removed.

Next Steps

The then Minister for Health, the Hon Greg Hunt MP, agreed to these recommendations on 29 March 2022. The implementation of these recommendation is currently being considered and progressed by the Department of Health and Aged Care in consultation with sponsors, treating physicians and patient advocacy groups.