# Life Saving Drugs Program (LSDP) 24 month-like Review Summary: elosulfase alfa (Vimizim®)

## Introduction

Elosulfase alfa is an enzyme replacement therapy for the treatment of Mucopolysaccharidosis Type IVA (MPS IVA), also known as Morquio A syndrome. It was listed on the LSDP on 1 August 2017. The LSDP Expert Panel (Expert Panel) agreed at its
October 2021 meeting that a 24 month-like review should be undertaken when the current funding arrangement expired.

## Purpose of the 24-month review

Following a decision of Government in 2018, all new medicines made available on the LSDP are subject to reviews of usage and financial costs 24 months after listing.

The purpose of these 24-month reviews 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 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. The Expert Panel is responsible for commissioning the reviews and making recommendations to the Chief Medical Officer (CMO).

This review aimed to undertake an 24 month-like review assessment of elosulfase alfa for the treatment of MPS IVA. This review was considered by the Expert Panel at its October 2022 and February 2023 meetings.

## Terms of Reference

Full Terms of Reference (ToR) and protocol questions are at Attachment A.

### ToR 1 – Clinical effectiveness and Safety

This ToR aimed 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 elosulfase alfa on the LSDP, to inform judgements regarding the comparative clinical effectiveness and safety of elosulfase alfa. The new evidence needed to be presented in the context of previous evidence considered by the Pharmaceutical Benefits Advisory Committee (PBAC) and the Expert Panel.

### ToR 2 – Test Validity and Utility

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

### ToR 3 – Utilisation and Consumer Impact

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

### ToR 4 – Financial Impact

This ToR aimed to review the value for money of elosulfase alfa under the current funding arrangements and future implications of the current listing of elosulfase alfa on the LSDP.

## Main issues for consideration

### ToR 1 – Clinical Effectiveness and Safety

At the time of the review there were XX patients registered for treatment with elosulfase alfa on the LSDP of whom XX had ever received elosulfase alfa, and with XX actively receiving treatment with elosulfase alfa. The median time on treatment was 4.6 years. Treatment was not ongoing in XXX patients due to death and XX patients due to family choice. XXX patients applied to the program but never commenced treatment.

There were few patients with missing doses, and doses were missed primarily due to family illness or travel. Data on the expected versus actual supply are not available in the LSDP, and as such analysis of the timing of interrupted treatment or its impact was not possible.

The clinical effectiveness of elosulfase alfa is assessed using the 6 minute walk test (6MWT), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), urinary keratan sulfate (uKS) and left ventricular ejection fraction (LVEF). While the use of these parameters was supported by the literature, clinician and consumer consultation suggested that these methods, while objective, may not be the best methods for determining efficacy as they do not take a holistic approach to assessing effectiveness.

In the studies considered in the literature review, in general, improvements in the 6MWT were modest, and were significant in some but not all patients. Only minimal changes in FVC and FEV1 were observed. There were significant reductions in uKS following elosulfase alfa commencement, and LVEF appeared to be maintained. Quality of life appeared to improve following elosulfase alfa commencement, particularly in the mobility and self-care domains.

For LSDP patients, there was significant heterogeneity in 6MWT results. Of the XX patients with available data, XX had improvements in their 6MWT distance. The majority had stabilisation or improvements in FVC and FEV1. Of the XX patients with uKS data, XXX had either a stabilisation or a marked improvement in uKS. There were improvements in LVEF in half of the patients enrolled on the LSDP. Those with reductions tended to have <10% change in LVEF.

In terms of survival and quality of life, XX LSDP patients have died. Significant improvements in mobility and MPS-HAQ were reported in the non-randomised MOR-005 study. No quality of life data are collected from patients enrolled in the LSDP.

The majority of patients experienced one or more adverse events, and hypersensitivity and infusion related reactions are common. Clinicians and patients reported that, although frequent, these were usually easy to manage.

### ToR 2 – Test Validity and Utility

A diagnosis of MPS IVA disease is based on elevated uKS, a deficiency in N‑acetylgalactosamine-6-sulfatase (GALNS) in white blood cells or skin fibroblasts and/or identification of 2 pathogenic mutations in the *GALNS* gene.

Initial treatment with elosulfase alfa may commence based on elevated uKS and deficiency of GALNS, however, genetic testing for mutations in the *GALNS* gene is to be performed in a NATA‑accredited laboratory for confirmation of diagnosis of MPS IVA within 6 months of commencement of acceptance into the program, with the results reported to the LSDP.

Diagnosis of MPS IVA can be challenging, and diagnostic delay and misdiagnosis is common. Not all patients have 2 identifiable pathogenic variants, and novel mutations are common.

Some alternative methods of diagnosis have been proposed. The first is spot urine tests that quantify a chondroitin sulfate (CS)-disaccharide (HNAc-UA). This assay may be useful for detecting response to enzyme replacement therapy (ERT). The second is quantifying the chondroitin sulfate non reducing end (CS NRE) using glycan isotope labelling liquid chromatography mass spectroscopy (GRIL-LC/MS) method. The authors of the assay study recommended that the CS NRE assay could complement the uCS NRE assay (i.e. the spot urine test).

Urine mucopolysaccharidosis substrate (uMPSs) analysis via mass spectroscopy has been proposed as a substitute for the uKS test for the LSDP reapplication process and for response assessment. Methods for such mass spectrometric approaches have been successful with 100% sensitivity and 100% specificity for identifying patients with MPS IVA. The method also has been used for longitudinal monitoring of patients with MPS, although to date reports have been specific to MPS I and VI. The questions around whether the requirement for continued eligibility by a 20% change from baseline using the mass spectroscopy test could not be answered based on available literature. It was postulated that given the potential for significant reductions in urinary glycosaminoglycans (uGAGs) seen in MPS I and MPS VI, it might be feasible also in this setting. There was some evidence that uKS does not completely normalise even with ERT in people with MPS IVA. In terms of how response can be assessed using mass spectroscopy for patients who have a baseline uKS result, there was a moderate correlation between uKS measurements with LC/MS/MS methods (r=0.666, p<0.001).

The prevalence estimates reported in the literature searches for MPS IVA appeared similar to those reported in the original PBAC submission. Aside from an initial peak in uptake of elosulfase alfa on the LSDP at the commencement of the program, there did not appear to have been any increase in rate of diagnosis of MPS IVA.

Approximately XXXX of MPS IVA patients in the LSDP commenced treatment under the age of 5 years, and therefore were not required to have 6MWT or FVC tests. Therefore, these tests may not have appropriate utility for the LSDP. Despite this concern, there is no readily available alternative, other than a clinician or patient global assessment, which is subjective and prone to bias.

No new treatments for MPS IVA have become available since 2017.

### ToR 3 – Utilisation and Consumer Impact

It was anticipated that the appropriate population is being treated with elosulfase alfa, although clinical records do not always show compliance with eligibility criteria.

96% of patients who applied to the LSPD for treatment with elosulfase alfa have documentation of a diagnosis of MPS IVA, by the criteria stipulated by the LSDP (with the caveat that in a small minority of patients, reporting to the LSDP of mutational status was delayed). The remaining patient did not commence treatment. XX% of patients with recorded outcomes over time on treatment satisfied the requisite improvement in 3 out of 4 clinical parameters.

The number of patients receiving elosulfase alfa on the LSDP at the time of the review was below but broadly in line with expectations at the time of listing (XX currently on treatment compared to an estimated XX).

Elosulfase alfa was first listed on the LSDP on 1 August 2017. Most patients diagnosed with MPS IVA receiving treatment with elosulfase alfa on the LSDP at the time of the review were pre-school or school aged children. The median age of diagnosis was XXXX years, the median age of joining the LSDP was XXXX years, and the current median age of patients was XXXX years.

The LSDP was estimated to have increased the number of MPS IVA patients receiving treatment by XX patients.

Families with a member receiving elosulfase alfa on the LSDP make substantial financial and lifestyle sacrifices to access treatment. However, overall patients reported a positive experience in receiving their weekly treatment, and families believed sacrifices were outweighed by the benefits that patients received. Quality of life related impacts mattered most to families, rather than the parameters monitored by clinicians and reported to the LSDP. Families would like improved access to home infusions to minimise negative impacts of treatment on family life. The Product Information for elosulfase alfa does permit home infusion, but the sponsor does not have a home infusion program. A small number of patients access home infusion through hospital services.

The exclusion criterion for patients who miss more than 3 infusions in a 14-month period (excluding medical reasons) appeared poorly supported. Exclusion from treatment may be better predicated on predictors of poor patient responsiveness. The only XX patients that missed the threshold number of infusions without a medical reason each responded positively to 3 of the 4 clinical parameters over the course of their treatment. The secretariat noted that the rationale for this criterion appears to be based on the initial clinical trials, and was also a requirement in the NICE Managed Access Arrangement.

### ToR 4 – Financial Impact

The Expert Panel considered matters relating to the pricing of elosulfase alfa. These matters are subject to commercial in confidence arrangements.

Given dosage is patient age/weight/condition-specific, there is medicine supplied to patients over the prescribed dose due to the limitation of elosulfase alfa to 5mL vial sizes when the required dose does not round to 5mLs. The report estimated, in 2021, XXXX mL were supplied in excess of the millilitres prescribed. Single millilitre packaging is not available, and would likely be less cost effective to produce and supply. If wasted millilitres from all vials were combined, it would be equivalent to XXX 5mL vials, valued at $XXXXXX. The total expenditure in 2020-2021 was estimated to be $XXXXXX thus supply of elosulfase alfa over the prescribed dose equates to approximately 2.5% of medicine supplied.

## Expert Panel Recommendations

The Expert Panel made the following recommendations in relation to elosulfase alfa:

1. That the report provided by the reviewer and updated by the LSDP secretariat be accepted and considered final, noting that the data gaps in the report did not limit the Expert Panel’s ability to form recommendations.
2. That the initial eligibility criteria and mandatory ongoing assessments for MPS IVA be updated:
	1. the requirement for assessment of 6MWT, FVC/FEV1 and cardiac function (ECHO result) for eligibility is to be removed. In line with this, the requirement for the assessment of 6MWT, FVC/FEV1 and cardiac function (ECHO results) during treatment is to be removed.
	2. the biochemical test (i.e. uKS test or uMPSs) will be required at the following timepoints:
		1. at diagnosis (to establish a baseline)
		2. 1 to 3 months post initiation
		3. if a 20% reduction is not shown at (ii) – 6 months post initiation.
3. That the ongoing eligibility criteria be updated:
	1. the requirement for the assessment of uKS (beyond that required in 2b), 6MWT, FVC/FEV1 and cardiac function (ECHO results) is to be removed. Only a clinic letter will be required, but this should include the results of any of these tests if performed as part of standard care. All standard continuation and exclusion criteria for an LSDP medicine will remain.
	2. the exclusion criterion for missed infusions be removed.
	3. for patients who do not have at least a 20% reduction from baseline by the 6 months post-treatment initiation timepoint, the treating physician will be required to submit a clinic letter describing how the patient is responding to therapy and include any available supportive documentation for the department’s assessment.
4. That the Department renegotiate the Deed of Agreement with the sponsor to achieve a more favourable cost to Government for elosulfase alfa XXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXX. XXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX.

## Next Steps

The CMO has agreed to these recommendations. The implementation of these recommendations is currently being considered and progressed by the Department of Health and Aged Care in consultation with the sponsor, treating physicians and patient advocacy groups.