Life Saving Drugs Program (LSDP): Review of Medicines for Fabry disease

Review summary and expert panel recommendations

Purpose of the Fabry disease review

There are currently three medicines for Fabry disease listed on the LSDP: agalsidase alfa (Replagal®), agalsidase beta (Fabrazyme®), and migalastat (Galafold®). This Fabry disease review considered the two enzyme replacement therapies (ERTs), agalsidase alfa and agalsidase beta, which were listed on the LSDP for Fabry disease on 1 July 2004. The Expert Panel considered this review at its October 2020 meeting. Migalastat, which was listed on the LSDP on 1 November 2018, was out of scope for this review.

The review of Fabry disease medicines sought to develop a better understanding of the current use of these medicines by comparing current use against the recommendations and expectations at the time of listing.

The review further aimed to assess the clinical benefits achieved by using these medicines; ensure the ongoing viability of the LSDP; and ensure testing and access requirements for the medicines remain appropriate. It identified immediate and future changes that may be required to the funding criteria for Fabry disease medicines 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).

Fabry disease review terms of reference

1. Review the prevalence of Fabry disease within Australia.
2. Review evidence for the management of Fabry disease and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of these medicines on the program (including the validity of the tests).
3. Review clinical effectiveness and safety of medicines and evaluate the evidence of comparative effectiveness of LSDP Fabry disease medicines. This will include 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 Fabry disease.
5. Conduct an analysis of the value for money of LSDP Fabry disease medicines under the current funding arrangements.
6. Review the utilisation of LSDP Fabry disease medicines, including the way they are stored and dispensed, 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 Fabry disease within Australia

The prevalence of Fabry disease was estimated to be 0.87 per 50,000 people, meeting the definition of a rare disease for the purposes of the LSDP. The Expert Panel noted the prevalence of Fabry disease in Australia is rising over time, as is the number of patients with Fabry disease accessing treatment via the LSDP. Estimates of prevalence are becoming more complete due to greater awareness of the disease and pathology associated with it, advances in diagnostic technology, and cascade testing of family members, all of which increase the rate of diagnosis of Fabry disease. Should widespread subsidised genetic testing or newborn screening be introduced, diagnosis of Fabry disease could increase considerably. If the prevalence of Fabry were to increase, this may impact the eligibility of these medicines for the LSDP.

Approximately 30 per cent of patients with Fabry disease in Australia were estimated to have symptoms of end-organ damage and therefore were eligible for access to LSDP-subsidised treatment under current eligibility criteria. The majority (approximately 85 percent) of these eligible patients with Fabry disease were accessing treatment through the LSDP.

Recommendation 1:

The Expert Panel considered that Fabry disease met the prevalence criterion of less than 1:50,000 and on that criterion currently remained suitable for inclusion on the LSDP.

The Expert Panel noted that improved diagnosis and widespread testing was likely to increase both the prevalent number of people diagnosed with Fabry disease and increase the uptake of the Fabry medicines available on the LSDP. There was a potential for the prevalence of Fabry disease to exceed the 1:50,000 threshold prevalence criterion for eligibility for inclusion of therapies on the LSDP.

Given the increasing prevalence of Fabry disease in Australia, the Expert Panel recommended that the prevalence of Fabry disease be reviewed within five years, or within five years post implementation of any Government agreed changes to eligibility, to determine whether Fabry disease continues to meet the definition of a rare disease for the purposes of this program.

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

The Review found the current LSDP patient eligibility criteria and guidelines (for both initiating and ongoing patients) appeared to be more restrictive than those internationally, particularly for paediatric patients.

In Australia, only patients with evidence of end-organ damage are eligible for treatment, whereas international clinical guidelines recommended initiating treatment in asymptomatic patients with ‘classic’ Fabry disease (i.e. patients with α-Gal-A enzyme activity <5 percent). In addition, the Review found some of the initiation and continuation criteria may no longer

be justified. However, the Expert Panel noted that the cost:benefit ratio associated with treatment in any additional cohort of patients may not be consistent with the cost:benefit ratio associated with treatment that applies in the currently eligible population, or with that used to inform the original decision for listing on the LSDP.

The Expert Panel indicated it would welcome proposals from sponsors to revise the eligibility criteria for access to treatment (including criteria for continued access) to more closely align with international clinical guidelines and clinical evidence. The Expert Panel advised such proposals should include an assessment of the clinical, economic and financial implications if expanded access is a likely consequence of the adoption of any proposal.

The Expert Panel acknowledged the lack of funding for investigations used to diagnose and monitor Fabry disease. The Expert Panel noted the LSDP is not the appropriate program for providing funding for such tests. The Expert Panel further noted the Medical Services Advisory Committee (MSAC) provides advice to Government on the health technologies and services that may be publicly funded through the Medical Benefits Schedule. Applications requesting subsidy of investigations used to diagnose and monitor Fabry disease may be submitted to MSAC.

Recommendation 2:

The Expert Panel recognised that LSDP patient eligibility treatment criteria were not currently aligned with International Clinical Guidelines.

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 medicines for the treatment of Fabry disease. Sponsor submissions must include an assessment of the clinical, economic and financial implications if expanded access is a likely consequence of the adoption of any proposal.

Recommendation 3:

The Expert Panel agreed that the purpose, clinical benefits and frequency of undertaking specific diagnostic/clinical monitoring tests should be reviewed and clarified. The Expert Panel noted the importance of considering analytical validity, clinical validity, and clinical utility when assessing the value of health technologies used in the diagnosis and in monitoring patients with Fabry disease.

Treating physicians are best placed to provide input on the usefulness of current tests used to diagnose, manage and monitor paediatric and adult Fabry LSDP patients.

The Expert Panel recommended that a reduction in the frequency of some tests should be considered to reduce the burden on patients. The Expert Panel recommended further clinical advice be sought for review of the following diagnostic/ongoing clinical tests in relation to their places in LSDP program requirements:

- Blood spot enzyme testing for diagnosis, as a replacement for the enzyme activity test.
- Timed overnight urine collection as an alternative to 24-hour collection for testing protein excretion in all patients with renal disease.
- Estimated glomerular filtration rate (eGFR) as an alternative measure of chronic kidney disease to kidney biopsy for all patients with suspected renal disease.
- Should there be a requirement for annual cardiac MRIs for patients entering under the cardiac criterion?
- Should there be a requirement for respiratory function tests?
- Which instruments should be used by the LSDP to assess pain and quality of life?

ToR 3 – Review clinical effectiveness and safety of medicines and evaluate the evidence of comparative effectiveness of LSDP Fabry disease medicines. This will include analysis of LSDP patient data and international literature to provide evidence of life extension

The Review found comparisons of outcomes reported in more recent studies with outcomes reported in studies presented to the Pharmaceutical Benefits Advisory Committee (PBAC) were likely to be confounded due to improvements in general supportive care. Nevertheless, benefits observed with each of the therapies in terms of impact on renal, cardiac, pain and quality of life outcomes appeared to be broadly consistent with those expected at the time the therapies were considered by the PBAC.

The Expert Panel accepted the improvements observed in these outcomes would be likely to result in improved survival; however, the relationship between the outcomes assessed and survival has not been well characterised. The Expert Panel noted the mean age of death was higher in studies of ERT-treated patients with Fabry disease than in untreated patients with Fabry disease. Although ERT was likely to have been a significant contributor to improvements in survival, full attribution of the observed improvement to the use of ERT was unreasonable given limitations of the available evidence and improvements in standards of care. The magnitude of the improvement in survival due to ERT use was therefore considered highly uncertain.

The available evidence provided no objective basis for changing the previous conclusion made by the PBAC with respect to comparative effectiveness. The PBAC had found "*there is insufficient evidence to support a conclusion that there is any clinical difference between agalsidase alfa and beta at the registered doses".*

Recommendation 4:

Based on the evidence identified through the Review, the Expert Panel recommended that agalsidase alfa and agalsidase beta appear to extend survival and thus remain suitable for listing on the LSDP.

The Expert Panel considered that there was insufficient evidence to support any claim of a clinically important difference between agalsidase alfa and agalsidase beta, the two LSDP funded medicines for Fabry disease.

ToR 4 – Review relevant patient-based outcomes that are most important or clinically relevant to patients with Fabry disease

Consultations with consumers and other stakeholders broadly indicated the outcomes that are most important to patients include improvement in symptoms (which affect quality of life (QoL)). Clinicians agreed that slowing the progression of disease and increasing life expectancy were important outcomes.

Substantial gaps in the current collection of outcomes data from LSDP patients were noted, and this limited interpretation of the worth of measuring specific outcomes.

The Expert Panel considered that a closer examination was necessary to determine:

i. which endpoints warrant data collection
ii. what data are required to assess those endpoints
iii. what the appropriate approaches to collection of those data are; and
iv. design of a statistical plan to analyse these data.

The aim of this closer examination would be to limit data collection while improving monitoring and meaningful reporting of key outcomes for patients treated through the LSDP.

Recommendation 5:

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 relating 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; and

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

The LSDP should implement a streamlined solution that enables clinicians to enter patient data both for everyday administration of the program and for future medicines reviews. The Expert Panel recommended that this revised approach should improve clinician and patient satisfaction and facilitate availability of complete and comprehensive data for any future reviews of Fabry medicines.

ToR 5 – Conduct an analysis of the value for money of LSDP Fabry disease medicines under the current funding arrangements

Significant price reductions have occurred for agalsidase alfa and agalsidase beta since the time of listing on the program. Despite this, the cost per patient per year of treatment remains high (on average $[redacted]/patient/year).

The Review's calculated estimate of survival gain in ERT-treated versus untreated patients was based on a comparison of survival among patients in natural history studies and those on the LSDP. The average life years gained per treated patient was approximately eight years. While this estimate had a high degree of bias due to limitations in both datasets, the survival gain seen was substantially less than estimated at the time of listing. The incremental cost-effectiveness ratio was estimated at $[redacted] per life year gained. This estimate was associated with significant uncertainty but did indicate that there was a very high cost paid for the health gains achieved.

There was no evidence to indicate a difference between the two treatment options and therefore the cost minimisation approach between the two medicines remained appropriate.

Recommendation 6:

The Expert Panel noted that there appeared to be a survival gain and improvement in quality of life from treatment with agalsidase alfa and agalsidase beta, and that the cost of these medicines remained very high. The Expert Panel therefore recommended that the pricing and listing arrangements for these medicines 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 Fabry Disease are considered for entry onto the LSDP or other subsidy programs; and/or

(iii) changes in eligibility criteria are being considered.

Should the value for money of any LSDP medicine approach a level that could be considered cost effective in terms of Pharmaceutical Benefits Scheme (PBS) listing, the medicine should be reconsidered for suitability on the PBS.

ToR 6 – Review the utilisation of LSDP Fabry disease medicines, including the way they are stored and dispensed, and evidence of patient compliance to treatment.

Consultation with patients and clinicians indicated that, in practice, weight-based doses are rounded to the nearest whole vial of drug and the entire contents of the vials are administered to patients. The Expert Panel did not object to the practice of prescribing and approving dosages in whole vials. However, the Expert Panel noted there is more drug administered than recommended or approved (when considering the dose administered versus the approved weight based recommended dose) with agalsidase alfa compared with agalsidase beta. This arises because agalsidase alfa has only one vial size whereas agalsidase beta is available in two vial sizes, enabling dosing closer to weight-based recommendations. This resulted in a higher associated difference in cost between approved and administered dose.

Recommendation 7:

The Expert Panel considered that the value for money aspects of weight based dosing be reconsidered. Specifically, the funding approach to treatment at above recommended and approved medicine levels should be reassessed. The Expert Panel were of the view

that the Commonwealth should only be reimbursing for the dose of drug prescribed by the treating physician within the approved Product Information doses. To account for this, renegotiation of the funding arrangements with medicine sponsors may be required.

The Expert Panel acknowledged the challenges for sponsors in providing product to satisfy the requirements of different international markets but recognised the significant difference between the amount administered and the amount recommended, and the related additional cost involved in the administration of agalsidase alfa compared with agalsidase beta. The Expert Panel recommended that the sponsor of agalsidase alfa should be requested either to make a smaller vial available or to adjust pricing of the single vial to account for use of agalsidase alfa in excess of the weight-based dose approved in the Product Information.

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

Based on the evidence, the Expert Panel noted additional ERT, oral substrate reduction, and gene therapies for patients with Fabry disease were in clinical development. The Expert Panel noted availability of these may have an impact on the LSDP-funded market of medicines for Fabry disease.

Recommendation 8:

The Expert Panel noted that novel therapies are in development and their availability may impact the LSDP and patients in the future, however none of these therapies were imminent.

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.