



Life Saving Drugs Program (LSDP): Review of Medicines for Pompe Disease

Review summary and Expert Panel recommendations

Purpose of the Pompe Disease Review

Alglucosidase alfa (Myozyme®) was listed on the LSDP for:

- infantile onset Pompe disease (IOPD) on 1 February 2010;
- juvenile onset Pompe disease (JOPD) on 1 February 2015; and
- adult onset Pompe disease (AOPD) on 1 September 2015.

The Expert Panel considered this review at its October 2020 meeting.

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

The review further aimed to assess the clinical benefits achieved through the use of alglucosidase alfa; ensure the ongoing viability of the LSDP; and ensure testing and access requirements for alglucosidase alfa remain appropriate. It identified immediate and future changes that may be required to the funding criteria for alglucosidase alfa 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 (ToR). The ToRs were tailored specifically to each disease and the relevant medicine(s).

Pompe Disease Medicine Review Terms of Reference

1. Review the prevalence of Pompe disease within Australia, both split by type (infantile onset, juvenile late-onset, adult late-onset) and overall.
2. Review evidence for the management of each type of Pompe 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 alglucosidase alfa in each of the treated populations, 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 each type of Pompe disease.
5. Assess the value for money of alglucosidase alfa in each of the treated populations under the current funding arrangements by evaluating the benefit of the medicines' treatment outcomes and cost.
6. Review the utilisation of alglucosidase alfa in each of the treated populations 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 Pompe disease within Australia, both split by type (infantile onset, juvenile late-onset, adult late-onset) and overall.

The prevalence of Pompe disease was estimated to be 0.18 cases per 50,000 people. The Expert Panel noted there was a paucity of data regarding the prevalence of Pompe disease in Australia. The observed prevalence of Pompe disease appears to be growing faster than the general Australian population, particularly since the introduction of LSDP subsidised treatment for juvenile and adult onset Pompe diseases in 2015.

Due to eligibility criteria limiting the use of available treatment to patients with symptoms of end organ damage, approximately 96 percent of patients with Pompe disease in Australia were estimated to be eligible for access to treatment. The majority (80 to 85 percent) of these eligible patients were accessing alglucosidase alfa on the LSDP. The Expert Panel noted these estimates did not consider any IOPD patients that do not proceed to treatment.

Recommendation 1:

The Expert Panel considered that Pompe disease met the prevalence criterion of less than 1:50,000 and remained suitable for inclusion on the LSDP. Due to the increasing prevalence of Pompe disease in Australia, the Expert Panel recommended that the prevalence of Pompe disease be reviewed within five years post implementation of Government agreed changes to determine whether Pompe disease continues to meet the LSDP definition of a rare disease.

ToR 2 – Review evidence for the management of each type of Pompe 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 classification of Pompe (IOPD, JOPD, and AOPD) appears to be different to international clinical guidelines which use “classic” and “late onset adult” disease. The Expert Panel did not consider this difference adversely impacted access or usage.

The LSDP patient eligibility criteria and guidelines were based upon low GAA enzyme activity and molecular testing for GAA disease-causing mutations, which was consistent to international clinical guidelines, and also included a third criterion – elevated tetrasaccharide level. Treating physicians are required to provide results for two out of these three tests. The Expert Panel considered the effect of removing the elevated tetrasaccharide criterion was uncertain, noting it was not essential for treatment initiation and so was unlikely to reduce access. The Expert Panel noted stakeholders were not supportive of removing this criterion.

Asymptomatic patients with JOPD had earlier access to subsidised treatment than international clinical guidelines suggest, as LSDP eligibility required a diagnosis but not presentation of symptoms. The Expert Panel noted the number of patients with JOPD was small. As there was only a small number of JOPD patients accessing LSDP medicines, the Expert Panel proposed streamlining the eligibility criteria to include two tiers, IOPD and later onset Pompe Disease (LOPD), to align with international classifications.

The Expert Panel found that some of the continuation criteria for LSDP eligibility may not be warranted, noting many monitoring tests for Pompe and/or responsiveness to treatment are not routinely conducted/reported to the LSDP, and it is uncertain whether they have resulted

in cessation of therapy. Testing also increases the burden for patients and costs to the healthcare system.

Recommendation 2:

The Expert Panel noted that the international classification of Pompe disease is for classic and later-onset disease. The Expert Panel advised that the current classification of IOPD, JOPD and AOPD should be revised to include only IOPD and LOPD.

Recommendation 3:

The Expert Panel advised that the initial LSDP patient eligibility requirements appear to be suitable for appropriate patient access to treatment.

Recommendation 4:

The Expert Panel acknowledged the importance of analytical validity, clinical validity, and clinical utility when considering the value of health technologies. The Expert Panel agreed that the purpose, clinical benefits and frequency of undertaking specific diagnostic /clinical monitoring tests 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 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:

- For IOPD: the need for annual psychometric testing, full neurological testing and testing of haemoglobin, platelets, alanine amino transferase, aspartate amino transferase and lactate dehydrogenase.
- For IOPD: clarification on what constitutes 'invasive ventilation'.
- For children under the age of 12: remove requirement for FVC and 6MWT.
- For AOPD: need for manual muscle testing in AOPD.

ToR 3 – Review clinical effectiveness and safety of alglucosidase alfa in each of the treated populations. This will include analysis of LSDP patient data and international literature to provide evidence of life extension

The Expert Panel noted the outcomes observed from alglucosidase alfa (including pulmonary function, cardiac, growth and motor outcomes) appear to be approximately consistent with those expected at the time of listing.

The Expert Panel accepted the improvements observed in these outcomes would be likely to result in improved survival. It noted mean age of death was higher in treated than untreated patients with Pompe disease (for all three subtypes). However, the relationship between the

outcomes assessed and survival was not clear. Comparison of survival in treated versus untreated patients was subject to potential bias, making the size of the improvement in survival highly uncertain.

Recommendation 5:

The Expert Panel advised that on the basis of the evidence identified through the Review, alglucosidase alfa remains suitable for listing on the LSDP.

ToR 4 – Review relevant patient-based outcomes that are most important or clinically relevant to patients with each type of Pompe disease

The Expert Panel noted that consultations with patients indicated reduced mobility, pain, shortness of breath, fatigue and drowsiness were the most important outcomes. Treating physicians also emphasised life expectancy as an important outcome. Stakeholder consultation indicated patients across all three subgroups report improved quality of life due to treatment with alglucosidase alfa.

Substantial gaps in the collection of data from LSDP patients were noted, and this limited interpretation. The Expert Panel discussed 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 that 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 6:

The Expert Panel noted that the extent and methods of data collection and the approach to analysis of the data require improvement. The availability of consistent and complete data extracted from initial and ongoing applications to the program is essential. 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 medicines reviews. The Expert Panel recommended that this revised approach should see a future review of alglucosidase alfa with complete and comprehensive data resubmitted for its consideration.

ToR 5 – Assess the value for money of alglucosidase alfa in each of the treated populations under the current funding arrangements by evaluating the benefit of the treatment outcomes and cost.

The Expert Panel noted each subtype of Pompe disease currently has a different pricing arrangement and therefore associated cost/Life Year Gained (LYG):

Subtype of Pompe disease	Cost per patient (ex GST) per month	Cost/LYG
IOPD	██████	██████
JOPD	██████	██████
AOPD	██████	██████

The Expert Panel noted the significantly higher cost per patient for JOPD compared to IOPD and AOPD and discussed whether these pricing arrangements reflected value for money in each patient group. It considered an alternative pricing structure could be negotiated with the sponsor, reflecting the recommended change from the existing three tier classification system to the new two-tier classification system.

The Expert Panel noted there were no estimates of Incremental Cost Effectiveness Ratio based on Quality Adjusted Life Years or LYG included in the PBAC submission for IOPD; however, there was indirect evidence of increased survival in patients receiving treatment. For late onset (JOPD and AOPD), the PBAC submission modelled a survival gain of 6.80 years with enzyme replacement therapy. In the literature, there was a lower mortality rate in treated patients. The Expert Panel noted that the Report determined there was an insufficient number of events to draw conclusions on survival benefits of alglucosidase alfa from the LSDP data.

Recommendation 7:

The Expert Panel noted that there appeared to be a survival gain and improvement in quality of life from treatment with the alglucosidase alfa, and that the cost of this medicine remained very high. Due to uncertainty of survival gains as a result of limited data, costs associated with alglucosidase alfa treatment may be even higher than current estimates. The Expert Panel therefore recommended that the pricing and listing arrangements for alglucosidase alfa 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 Pompe disease 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 alglucosidase alfa in each of the treated populations, including storage, dispensing and evidence of patient compliance to treatment.

The Expert Panel noted in the Report that patients with IOPD were prescribed the highest average dose per kg out of the three subtypes. However, the amount of medicine used in excess of the approved dose had been decreasing over time. Stakeholder consultation indicated the high doses were due to the often critical presentation of IOPD, particularly during a concurrent illness. The Expert Panel noted historically a small number of patients were approved for the use of an additional LSDP subsidised 20mg/kg dose (or doses) during their treatment which may account for the high average dose per patient. Pompe disease patients were largely compliant with treatment.

The Expert Panel noted the consumer group's concern that for JOPD patients, approximately 96 percent of the recommended dose was prescribed to patients on average. This may indicate a disconnect between the increasing weight of a young patient and the prescribed dose (which is weight dependent). The Expert Panel noted the LSDP can approve changes to a patient's dose throughout the year (i.e. not just at an annual reapplication) when notified in writing by the treating physician.

The Expert Panel also noted there is no home infusion program for alglucosidase alfa. While this is a sponsor driven service and outside the remit of the LSDP, the Expert Panel was supportive of the inclusion of Pompe Disease medicines in the home infusion program.

Based on the evidence presented in the Report, it was unlikely that there was utilisation outside the LSDP eligibility criteria for alglucosidase alfa. There was no evidence of storage variation or dispensing processes.

Recommendation 8:

The Expert Panel advised that the current weight based dose approved in the LSDP Pompe disease Guidelines remained suitable as it was in line with the Product Information and patients appeared to respond positively to treatment.

Recommendation 9:

The Expert Panel acknowledged that it can be difficult to maintain an accurate weight based dose for young growing patients. These patients, their families/carers and the healthcare staff providing the subsidised alglucosidase alfa to patients on a fortnightly basis should be mindful of a patient's changing weight and advise the treating physician of any changes. The Expert Panel noted that the current LSDP approval process for dose adjustments is administratively simple and that any improvements to the administration process (such as advised in Recommendation 6) should continue to incorporate a practical process for dose adjustment approvals.

Recommendation 10:

The Expert Panel advised that should the Product Information be formally updated to allow for home infusions of alglucosidase alfa, the Expert Panel and LSDP would be in support of amending the Pompe disease 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 additional enzyme replacement therapies and gene therapies for patients with Pompe disease were in clinical development, and there was one new medicine on the horizon that may impact the market for Pompe disease within the next two years. The increasing uptake of preconception genetic carrier testing may have an impact on the number of patients identified with Pompe disease.

The Expert Panel noted the availability of these therapies and testing may have an impact on the LSDP-funded market of medicines for Pompe disease.

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.