Australian Government

Department of Health and Aged Care

Life Saving Drugs Program (LSDP)

24 Month Review Terms of Reference and Protocol Questions:

Avalglucosidase alfa (Nexviazyme®) for the treatment of infantile-onset Pompe disease and late-onset Pompe disease

Background TO the review

The LSDP, administered by the Commonwealth Department of Health and Aged Care (the Department), was established in 1995 to provide people with ultra-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 18 life-saving high cost medicines for approximately 400 patients for the treatment of 11 ultra-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 the LSDP Expert Panel (the Expert Panel) 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.

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 24-month review of avalglucosidase alfa for the treatment of infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD).

AVALGLUCOSIDASE ALFA BACKGROUND

Avalglucosidase alfa was considered for listing on the LSDP at the February 2022 and June 2022 Expert Panel meetings. Following this consideration, the Expert Panel advised the CMO that avalglucosidase alfa for the treatment of IOPD and LOPD met the criteria for LSDP listing. The Minister for Health and Aged Care agreed to the listing and it was made available on the LSDP on 1 September 2022.

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 provided to 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, and any stakeholder input 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.

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.

TERMS OF REFERENCE

The 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 evaluation may provide further advice to the Expert 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 avalglucosidase alfa on the LSDP, to inform judgements regarding the comparative clinical effectiveness and safety of avalglucosidase alfa. The new evidence should be presented in the context of previous evidence.

Protocol Questions

Clinical effectiveness

- What additional evidence has been generated since the PBAC's prior consideration of avalglucosidase alfa regarding the impact of avalglucosidase alfa on the rate of progression of disease (including respiratory function, muscle weakness and sleep disordered breathing)? This should include:
    - New evidence from LSDP program data
    - New evidence from the literature (including overseas literature)
    - Consideration of how the evidence compares to expectations at the time avalglucosidase alfa was added to the LSDP
    - Consideration of implications of the new evidence.
- What are the most accurate methods for demonstrating efficacy of avalglucosidase alfa for patients with IOPD and LOPD disease on the LSDP?
- Is there evidence in the literature to suggest that changes in the eligibility criteria for the LSDP would be appropriate?

Safety

- What additional evidence has been generated since the PBAC's prior consideration of avalglucosidase alfa regarding the safety of avalglucosidase alfa, including in patients aged less than 12 months old? This should include:
    - New evidence from LSDP program data
    - New evidence from the literature (including overseas literature)
    - Consideration of how the evidence compares to expectations at the time avalglucosidase alfa was added to the LSDP
    - Consideration of implications of the new evidence.
- Adverse events:
    - Are the number and type of adverse events reported by patients on the LSDP, in post-marketing surveillance studies, and in the literature consistent with expectations arising from the data in the initial study presented to PBAC?

- How does the incidence of adverse events in patients treated with avalglucosidase alfa through the LSDP compare with the incidence of adverse events in the same patients who previously were treated with alglucosidase alfa on the LSDP?
- What is the impact of adverse events on patients and their carers, particularly within the context of parents' typical experience of managing their symptoms of IOPD or LOPD?
- If patient deaths occurred, what is the reported cause of each death (with differentiation of disease-related and treatment-related causes?

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 IOPD and LOPD disease who are candidates for treatment with avalglucosidase alfa.

Protocol Questions

Diagnosis and initial eligibility

- For patients receiving avalglucosidase alfa through the LSDP, what method has been used to confirm diagnosis of IOPD or LOPD?

  Diagnosis must have been made using one of the following methods:

  - Documented deficiency of acid alpha-glucosidase by prenatal diagnosis using chorionic villus biopsies and/or cultured amniotic cells; or
  - At least 2 of the following confirmatory diagnostic tests from a NATA-accredited laboratory:
  - *Documented deficiency of acid alpha-glucosidase in dried blood spot or lymphocytes or mixed leukocytes or skin fibroblasts or skeletal muscle.*
  - *Documented urinary tetrasaccharide testing indicating a diagnostic elevation of glucose tetrasaccharides.*
  - *Documented molecular genetic testing indicating a disease-causing mutation in the acid alpha-glucosidase gene (GAA gene).*

- For LOPD patients who commenced LSDP treatment aged 18 years and over, what additional criteria have been met to demonstrate eligibility? (Respiratory function test, sleep disordered breathing, significant muscle weakness)
- Are the existing eligibility criteria for access to avalglucosidase alfa on the LSDP fit for purpose?
- Given the current eligibility criteria, is the appropriate population being treated as intended at the time of listing?
- Did all patients currently receiving avalglucosidase alfa through the LSDP meet the initial eligibility criteria at the time of commencement on the program?
- Is there evidence in the literature to support treatment for LOPD following a genetic diagnosis in the absence of symptoms?

Ongoing Eligibility

- Do all patients currently receiving avalglucosidase alfa through the LSDP meet the ongoing eligibility criteria?

- Current continuation criteria for late-onset Pompe patients aged 18 years and over include a decline of less than 20% versus prior year on measures of 6 minute walk test (6MWT) or a decline of less than 10% versus prior year on measures of erect forced vital capacity (FVC). Should these specific percentage-based criteria be retained?
- Currently for LOPD patients aged 18 years and over, test results of 6MWT and FVC must be provided to LSDP at the first 6 months of initial treatment and thereafter annually. Should this requirement be retained?
- Are the outcomes measured in trials and assessed through the LSDP clinically important and/or important to patients/families?
- Would other measures of efficacy be more useful to clinicians in making ongoing treatment decisions?
- Are there other impacts of treatment with avalglucosidase alfa that patients/families identify as being important to any decision around ongoing treatment?

ToR 3: Utilisation and Consumer Impact

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

Protocol Questions

Utilisation

- Is the number of patients receiving treatment with avalglucosidase alfa on the LSDP consistent with expectations at the time of listing?
- What is the age distribution of patients diagnosed and treated with avalglucosidase alfa on the LSDP?
- Are patients who have accessed avalglucosidase alfa on the LSDP still receiving avalglucosidase alfa?
- Have any patients ceased or interrupted treatment with avalglucosidase alfa and, if so, why is treatment not ongoing?
- Has the introduction of avalglucosidase alfa increased the number of IOPD and LOPD patients seeking subsidised treatment on the LSDP beyond historical trends prior to availability of avalglucosidase alfa?
- What proportion of patients receiving treatment for IOPD and LOPD through the LSDP are being treated with avalglucosidase alfa compared to the alternative treatment alglucosidase alfa (Myozyme®)?
- What proportion of patients receiving avalglucosidase alfa have previously been treated with alglucosidase alfa through the LSDP?
- What proportion of avalglucosidase alfa patients are receiving their treatment through home infusion?
- What is the distribution of doses administered per administration across patients on the program?
- The TGA recommended dosage of avalglucosidase alfa is 20 mg/kg administered fortnightly. Dose escalation to 40mg/kg administered fortnightly may be considered for patients with IOPD who experience insufficient control or declining response at the lower dose. What

proportion of IOPD patients are receiving more than the TGA recommended dosage of 20 mg/kg?
- Have new treatments become available since 2022?

Incidence and Prevalence

- Has any additional evidence been generated since the LSDP Expert Panel's consideration of avalglucosidase alfa regarding incidence and prevalence of IOPD and LOPD?
    - Has there been an increase in diagnosis of Pompe disease in jurisdictions where screening has been introduced or increased?
    - Has prevalence increased since the availability of therapeutics, such as those on the LSDP?
    - What is the best current estimate of IOPD and LOPD in Australia?
- Pompe disease is currently being considered for inclusion in the national newborn bloodspot screening program. If Pompe disease is included in screened conditions, what is the estimated impact on LSDP utilisation of avalglucosidase alfa?
- If prevalence is increasing, are there implications for the supply chain of avalglucosidase alfa?

Consumer impact

- What (if any) changes in patient-relevant outcomes have been reported to due the availability of home infusion for avalglucosidase alfa?
- What (if any) negative impacts do patients experience during treatment with avalglucosidase alfa (for example out of pocket costs)?
- What (if any) changes in patient-relevant outcomes have been reported by patients treated with avalglucosidase alfa compared with alglucosidase alfa?
- What additional evidence has been generated since the sponsor's last submission to PBAC regarding the impact of avalglucosidase alfa on quality of life of patients and their carers?

ToR 4: Financial and Economic Impact

This ToR aims to review the value for money of avalglucosidase alfa under the current funding arrangements, including a review of the financial outcomes and future implications of the current listing of avalglucosidase alfa on the LSDP.

Protocol Questions

- What are the comparative total (to the program) and average per-patient costs?
    - Have these changed over time?
    - How do they compare with expectations at the time of listing consideration?
    - How do these costs compare with those of other LSDP drugs?
- What is the estimated incremental cost-effectiveness ratios (ICERS) per life-year gained (LYG) or per quality-adjusted LYG (QALY)?
- How do current estimated ICERs for avalglucosidase alfa in practice compare with estimated ICERs expected at the time of inclusion of avalglucosidase alfa on the LSDP?
- Have the arrangements under the deed of agreement provided adequate management of financial risk?