



## Life Saving Drugs Program – Avalglucosidase alfa (Nexviazyme<sup>®</sup>) outcome statement

### Summary of the consideration of the application from Sanofi Pty Ltd for the inclusion of avalglucosidase alfa (Nexviazyme<sup>®</sup>) on the Life Saving Drugs Program (LSDP) for the treatment of Pompe Disease

#### Overview:

The LSDP Expert Panel (the Panel) advises the Chief Medical Officer (CMO) on new medicine applications to the LSDP. Avalglucosidase alfa was considered for listing on the LSDP at the Panel's meeting on 18 February 2022, with further discussion at the Panel's meeting of 24 June 2022.

#### Background:

Avalglucosidase alfa is an enzyme-replacement therapy (ERT) approved by the Therapeutic Goods Administration (TGA) for use in patients with Pompe disease. Pompe disease is an autosomal recessive disorder caused by acid alpha glucosidase (GAA) deficiency. The GAA enzyme is essential for the degradation of lysosomal glycogen into glucose. A deficiency leads to accumulation of glycogen in multiple tissues. Accumulation of glycogen in lysosomes leads to enlargement and ruptures, which cause skeletal muscle destruction and progressive myopathy.

Pompe disease is classified into different phenotypes based on remaining enzyme level, age at onset of symptoms, extent of organ involvement and rate of progression to death. Pompe disease is classified as infantile-onset (IOPD) when symptoms present before the age of 1 year and late-onset (LOPD) for presentations from early childhood to adulthood. The most significant clinical manifestations of IOPD include progressive hypertrophic cardiomyopathy and muscle weakness, leading to cardiorespiratory failure. Without treatment, patients with IOPD typically die within the first year of life.

LOPD can be further classified as juvenile-onset (JOPD) (onset <18 years of age) and adult late-onset (AOPD) (onset ≥18 years of age). Following the Panel's Review of Pompe disease and in line with international guidelines, the classifications for Pompe disease used by the LSDP are now IOPD or LOPD. LOPD progresses more slowly than IOPD and is associated with a high burden of disease and significant morbidity resulting in poor quality of life. Patients present with impaired respiratory function and skeletal muscle weakness, especially limb girdle weakness, as the hallmark symptoms. With disease progression, patients often require walking devices or wheelchairs to assist with mobility and mechanical ventilation to help with breathing. Respiratory failure is the most common cause of death.

#### Pharmaceutical Benefits Advisory Committee (PBAC) Consideration

At its November 2021 meeting, PBAC considered a submission from Sanofi requesting the listing of avalglucosidase alfa on the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients with Pompe disease. PBAC did not recommend the requested Section 100 (Highly Specialised Drugs Program) listing of avalglucosidase alfa for the treatment of IOPD, JOPD or AOPD. PBAC considered that avalglucosidase alfa was not cost-effective at the proposed price and the extent of benefit to AOPD provided in the submission was uncertain. Further information on PBAC's consideration of avalglucosidase alfa, including reasons for rejection, is available in

## LSDP Expert Panel Consideration

### Funding Criteria

In order to be included in the LSDP, a medicine must be considered to meet each of the LSDP funding criteria A1-A8. A summary of the claims for avalglucosidase alfa against each criterion is presented below.

| LSDP criteria |                                                                                                                                                                                                                                          | How avalglucosidase alfa meets the criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <b>A1</b>     | <b>There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration (prevalence of ≤1 per 50,000 people).</b> | <p>The Panel concluded that Pompe disease meets prevalence criteria and remains suitable for inclusion on the LSDP through its Review of Pompe Disease.</p> <p>Avalglucosidase alfa is TGA approved for long term ERT for the treatment of patients 1 year of age and older with Pompe disease (acid α glucosidase deficiency).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>A2</b>     | <b>The disease is identifiable with reasonable diagnostic precision</b>                                                                                                                                                                  | <p>Pompe disease is identifiable through demonstration of a deficiency of acid alpha glucosidase (in dried blood spot, lymphocytes, or mixed leukocytes, or skin fibroblasts, or skeletal muscle), elevation of glucose tetrasaccharides in urinary testing and molecular genetic testing indicating a disease causing mutation in the acid alpha glucosidase gene (GAA gene), with two of three tests required for confirmation of diagnosis under the LSDP criteria.</p>                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>A3</b>     | <b>Epidemiological and other studies provide evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease</b>                                                           | <p>Untreated patients with IOPD typically experience devastating symptoms affecting the cardiovascular, respiratory and musculoskeletal systems. Without treatment, patients generally die from cardiorespiratory complications within the first 2 years of life.</p> <p>The course of JOPD is more slowly progressive. In younger children, it can present as delayed motor milestones, followed by progressive proximal muscle weakness with involvement of respiratory muscles. Death usually occurs because of respiratory failure before the end of the third decade.</p> <p>AOPD can present in the second to sixth decade of life as a slowly progressive proximal myopathy or, in approximately one third of cases, with symptoms dominated by respiratory insufficiency. Death in patients with either presentation usually results from respiratory failure.</p> |

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| <p><b>A4</b></p> | <p><b>There is evidence to predict that a patient’s lifespan will be substantially extended as a direct consequence of the use of the drug</b></p>                                                                                                                                                                        | <p>The survival gain from treatment with the existing LSDP treatment for Pompe disease, alglucosidase alfa (Myozyme®) was accepted prior to its initial LSDP listing for treatment of IOPD. More recently published studies and the LSDP data have shown survival exceeding historical data for untreated patients.</p> <p>A similar benefit in overall survival can be expected with avalglucosidase alfa, given that:</p> <ul style="list-style-type: none"> <li>• Avalglucosidase alfa is non-inferior to alglucosidase alfa based on efficacy measures of functional endurance, cardiac parameters, and pulmonary function tests, and has a similar safety profile.</li> <li>• As a rare disease, it is necessary to use surrogate outcomes relative to current treatment options.</li> <li>• It would be unethical to conduct a placebo controlled study.</li> <li>• Patients receiving ERT in a clinical trial setting are expected to survive duration of trial.</li> <li>• There is biological plausibility for at least similar effectiveness of avalglucosidase alfa and alglucosidase alfa; avalglucosidase alfa being modified to improve cellular uptake.</li> </ul> |
| <p><b>A5</b></p> | <p><b>The drug must be accepted as clinically effective but rejected for PBS listing because it fails to meet the required cost effectiveness criteria.</b></p>                                                                                                                                                           | <p>The PBAC considered avaglucoisidase alfa at the November 2021 meeting. The PBAC considered avalglucosidase alfa for LOPD, including the AOPD and JOPD populations, was likely non-inferior to alglucosidase alfa. The PBAC considered the lack of evidence for the IOPD population made the clinical claim of non inferiority for that population highly uncertain but that, overall, avalglucosidase alfa was likely to provide similar health outcomes to alglucosidase alfa. The PBAC considered avalglucosidase alfa was an effective treatment for IOPD and LOPD (compared to no treatment) but the extent of benefit was uncertain.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>A6</b></p> | <p><b>There is no alternative drug listed on the PBS or available for public hospital in-patients which can be used as life saving treatment for the disease. However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for inclusion on the LSDP.</b></p> | <p>There are no available alternative drugs on the PBS or non-drug therapeutic modalities which can be used as life saving treatment for Pompe disease.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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| A7 | <b>There is no alternative nondrug therapeutic modality (eg surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost-effective treatment for this condition.</b>                                 | There are no available alternative drugs on the PBS or non-drug therapeutic modalities which can be used as life saving treatment for Pompe disease.                                                                                                                                                                                                                                                                                                              |
| A8 | <b>The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one-year period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian.</b> | The TGA recommended dosage of avalglucosidase alfa is 20 mg/kg per fortnight. Dose escalation to 40 mg/kg every other week may be considered for patients with IOPD who experience insufficient control or declining response at the lower dose.<br><br>At the proposed avalglucosidase alfa price of \$ [REDACTED] per vial, the annual average treatment cost would be \$ [REDACTED], representing an unreasonable financial burden on the patient or guardian. |

## Pricing issues

Note that the price of all LSDP medicines are subject to commercial in confidence arrangements.

## Consumer Input

The Panel noted the consumer input from PBAC and the LSDP applications. The Panel found the insight provided by the stakeholders was informative and contributed to its deliberations.

## Treatment Guidelines

The application included draft Guidelines for the treatment of Pompe Disease through the LSDP, which proposed initial and ongoing eligibility requirements. The Guidelines proposed that diagnosis of infantile-onset or late-onset Pompe disease 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 National Association of Testing Authorities (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).
- The patient must satisfy, at the time of initial application, the following criteria to be eligible for treatment with avalglucosidase alfa:
  - the patient has a documented diagnosis of IOPD; or
  - the patient has a documented diagnosis of LOPD. Patients aged 18 years and over must also present with at least one of the following treatment

criteria:

- **Respiratory function test:** Patients with Forced Vital Capacity (FVC), either supine or erect, less than 80% of predicted value. Both supine and erect FVC should be performed.
- **Sleep disordered breathing:** Patients with an apnoea / hypopnoea incidence of >five events / hour of total sleep time or more than two severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study.
- **Significant muscular weakness:** Patients with significant muscular weakness as evidenced by Manual Muscle Testing (MMT) (employing the MRC score) of four or less in either limb girdle accompanied by a 6 Minute Walk Test (6MWT).

## Management of Uncertainties

To address uncertainties, clinical data will be collected through initial and ongoing applications to the LSDP. In line with LSDP policy and to manage uncertainties, a review of avalglucosidase alfa 24 months after listing will be conducted to ensure use and performance of the medicine is in line with the expectations at the time of listing.

### Context:

The LSDP provides access for eligible patients with rare and life-threatening diseases to essential and very expensive medicines. The LSDP provides eligible patients with access to these life-saving medicines at no expense to the patients or their families.

Before being considered for inclusion on the LSDP, a drug must first be considered by PBAC and accepted as clinically effective but rejected for PBS listing because it fails to meet the required cost effectiveness criteria.

All applications for new medicines seeking funding through the LSDP are considered by the LSDP Expert Panel. The role of the panel is to provide advice and assistance to the Chief Medical Officer (CMO) on a range of matters relating to new medicines seeking funding, including assessment of how the medicine addresses the LSDP criteria, guidelines for medicine use and testing requirements, suitable pricing arrangements, and data collection required for future reviews.

After receiving advice from the Panel, the CMO advises the Minister for Health and Aged Care on medicines proposed to be included on the LSDP.

This document aims to provide an overview of the evidence considered by the Panel and CMO during their assessment of medicines.

For more information on the process for new medicines seeking funding through the LSDP, refer to the LSDP Procedure guidance: <https://www.health.gov.au/resources/publications/procedure-guidance-for-medicines-funded-through-the-life-saving-drugs-program-lsdp>

### Sponsor's Comment:

Sanofi welcomes the Government's decision to list Nexviazyme (avalglucosidase alfa) on the LSDP. This is a significant decision for Pompe disease patients in Australia affected by this devastating disorder.