PHARMAC
Pharmaceutical Management Agency

31 January 2019

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Sanofi Genzyme
Australia

Via email: [redacted]

cc [redacted]
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Sanofi Genzyme

Via email: [redacted]

Dear [redacted]

Alglucosidase alfa advisory committee review

The application for alglucosidase alfa was considered by the Rare Disorder Subcommittee of PTAC at its meeting held on 5 & 6 November 2018. Please find below the record from that meeting.

Confidential information – please do not share until minute published by PHARMAC

Alglucosidase alfa for the treatment of Late-onset Pompe disease (LOPD)

Application

The Subcommittee reviewed an application from Sanofi Genzyme for the funding of alglucosidase alfa (Myozyme) for the treatment of late-onset Pompe disease.

The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

The Subcommittee **recommended** that the application for alglucosidase alfa for the treatment of late onset Pompe disease be **declined** based on the uncertainties regarding survival benefit, modest clinical benefits with regards to ambulation and pulmonary function, and the high proposed cost of the medicine.

The Subcommittee would welcome an application for alglucosidase alfa targeting treatment to those individuals considered to have juvenile-onset Pompe disease.

Discussion

The Subcommittee noted that PTAC had reviewed the evidence regarding the use of alglucosidase alfa for the long-term treatment of late-onset Pompe disease (LOPD) on a number of occasions between 2009 and 2017. The Subcommittee noted that PTAC had previously recommended alglucosidase alfa for LOPD be declined; PTAC had noted the significant unmet health need faced by patients with LOPD but considered that overall the evidence available did not demonstrate a clinically significant benefit

from treatment with alglucosidase alfa. PTAC considered that it is extremely difficult to determine which patients could potentially experience clinical improvement with enzyme replacement therapy (ERT) with alglucosidase alfa from currently available clinical data.

The Subcommittee noted that Pompe disease is a rare lysosomal storage disease caused by a deficiency of the lysosomal enzyme acid alfa-glucosidase (GAA), which results in the accumulation of glycogen in almost all tissues but predominantly skeletal muscle. The Subcommittee noted that LOPD is a multisystem disorder that typically manifests as limb-girdle muscle weakness, respiratory symptoms, and progression to respiratory insufficiency due to diaphragmatic and intercostal muscle weakness.

The Subcommittee noted a 2005 survey of Dutch patients (Hagemans et al. Brain 2005;128:671-7) which reported a mean age of symptom-onset of 28 years (±14.3 years), and that 18% of patients surveyed had symptoms before 12 years of age. Members noted that generally, patients experience loss of ambulation in their mid-forties.

The Subcommittee noted that life expectancy is reduced in patients with Pompe Disease. The Subcommittee noted that the median survival after diagnosis of 268 adult patients without ERT in the Pompe Register between 2002 and 2009 was 27 years, and that the estimated 5-year survival was 95% (Güngör et al. Orphanet J of Rare Dis. 2011;5:34). The Subcommittee noted that the estimated survival dropped to 83%, 65% and 40% at years 10, 20, and 30, respectively; and that the five-year survival for patients without a wheelchair or respiratory support was 95% compared with 74% in patients who were wheelchair-bound and required respiratory support.

The Subcommittee noted that the rate of progression and sequence of respiratory and skeletal involvement in LOPD is highly variable and appears to be related to disease duration rather than age.

The Subcommittee noted that there are two subtypes of Pompe disease: infantile-onset, which is diagnosed in the first year of life and causes serious disease including cardiomyopathy; and LOPD, where diagnosis is made at over one year of age or under one but without cardiomyopathy. Members noted that LOPD can present as early as the first decade of childhood, or as late as the sixth decade of adulthood, and that juvenile-onset Pompe disease is a subset of LOPD where onset occurs later in childhood or adolescence. Members noted that alglucosidase alfa has been listed on the Pharmaceutical Schedule for the treatment of Infantile-onset Pompe disease since December 2016 with criteria for patients up to 24 months of age; however, there are currently no patients on treatment.

The Subcommittee noted that there are no specific treatments for LOPD funded in New Zealand; clinical management involves treating the symptoms associated with limb-girdle muscle weakness, respiratory symptoms, and progression to respiratory insufficiency. The Subcommittee noted that this often requires a multidisciplinary approach due to the broad spectrum of clinical manifestations associated with LOPD. The Subcommittee noted this could include clinical management and rehabilitation to preserve motor function, lung function and minimise secondary complications, nutritional support, and surgical intervention to manage contractures.

The Subcommittee acknowledged the high health need of patients with LOPD, noting that the burden increases over time. Members noted that LOPD can have a high emotional and psychological impact on families and puts a significant burden on caregivers.

The Subcommittee considered that epidemiological data regarding the prevalence of LOPD disease in New Zealand indicates that there are currently nine patients in New Zealand with diagnosed LOPD. The Subcommittee noted that three of the diagnosed patients are of Māori ethnicity. Members noted that a number of patients with LOPD in New Zealand currently receive ERT as compassionate supply or via a clinical trial. The Subcommittee considered that these data indicate that the prevalence of Pompe disease is less than 1:50,000.

The Subcommittee noted that alglucosidase alfa is approved by Medsafe for the long-term treatment of Pompe disease in children and adults of all ages. The Subcommittee noted that alglucosidase alfa is not indicated for the treatment of any other condition.

The Subcommittee considered that the application for the funding of alglucosidase alfa met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

The Subcommittee noted that the recommended dosage of alglucosidase alfa is 20 mg/kg of body weight administered via infusion every two weeks over a period of four hours.

The Subcommittee noted that applications for the funding of alglucosidase alfa for the treatment of LOPD have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Canada (CADTH), Scotland (SMC), and UK (AWMSG) did not recommend the funding of alglucosidase alfa for LOPD, that Australia funds alglucosidase alfa through the Life Saving Drugs Program, and that the UK funds alglucosidase alfa for the treatment of LOPD through Orphan Drug Schemes.

The Subcommittee noted that previous PTAC considerations of the evidence were extensive and covered available data up to the end of 2016. The Subcommittee considered key evidence identified by the supplier that had previously considered by PTAC, as well as new evidence that has been published since the Committee's 2016 review.

The Subcommittee noted one systematic review and one cohort study that have been published since 2016.

The Subcommittee noted a publication of the 2017 European Consensus for starting and stopping ERT in adult patients with Pompe disease, which included a systematic review investigating the efficacy of ERT in adults with Pompe disease (van der Ploeg et al. Eur J Neurol. 2017;24(6):768-e31). The Subcommittee noted that data from one clinical trial and 43 observational studies, covering a total of 586 individual adult patients, provided evidence of a beneficial effect of ERT at group level; at the individual patient level, the response to treatment varied, but the factors associated with a patient's response to ERT were rarely described. The Subcommittee considered that survival benefit was not explored in sufficient detail in the analysis. Members considered that the publication provided useful information regarding starting and stopping criteria for ERT.

The Subcomittee noted a prospective cohort study conducted in the Netherlands which included 102 adult patients with Pompe disease (Kuperus et al. Neurology. 2017 Dec 5;89(23):2365-73). The Subcommittee noted that the median follow-up duration was 6.1 years (range 0.4 to 7.9 years), of which 5.0 years (range 0.2 to 7.3 years) were during ERT. The Subcommittee noted that the authors concluded that treated patients had better muscle strength, activity levels, pulmonary function, and improved daily life

activities compared to what would have been expected for their untreated disease course. The Subcommittee noted that the largest increase was seen during the first two to three years of treatment. Members questioned whether this indicated that the benefit of treatment may peak after the first few years of treatment and then decline.

The Subcommittee noted a systematic review and meta-analysis first considered by PTAC as an unpublished article in 2016 that was subsequently published in 2017 (Schoser et al. Neurology 2017;264:621-30). The Subcommittee noted that this meta-analysis examined the effect of ERT on survival, motor, and respiratory function; and assessed the effect of treatment on wheelchair use and ventilator status (although it did not draw any conclusions regarding wheelchair use and ventilator status). The Subcommittee noted that the meta-analysis used a variety of synthesis methods to evaluate data from 19 studies (438 patients) which had investigated the effect of alglucosidase alfa for the treatment of LOPD. Members noted that the analysis concluded that the risk of mortality in treated patients was reduced to close to one fifth of that experienced by untreated patients (a rate ratio of 0.21; 95% CI 0.11 to 0.41), and varying benefit was described across all other clinical outcomes. The Subcommittee considered the effect size appeared significant; however, the clinical significance of this effect was unclear. Members noted some concerns regarding the quality of the systematic review given the heterogeneity of the studies included and uncertainty regarding how the results were calculated. Members noted that PTAC had noted similar concerns in its 2016 review of the unpublished data.

The Subcommittee noted the results of a prospective survey which reported that ERT reduced the risk of wheelchair dependency in adult Pompe patients (van der Meijden et al. Orphanet J Rare Diseases 2018;13:82-4). The Subcommittee noted that data were collected as part of a prospective international survey, the IPA/Erasmus MC Pompe survey, which was conducted annually between 2002 and 2016. The Subcommittee noted the inclusion criteria for analysing the risk of wheelchair use were met by 189 patients (median age 47 years; range 18 to 75). The Subcommittee noted that during follow-up, 126 (67%) patients started ERT. The Subcommittee noted that over 1120 person-years of follow-up (median 5 years), 46 individuals became wheelchair dependent, 16 of whom used ERT; after adjustment for disease duration, sex and country, ERT was reported to reduce the risk of wheelchair use (HR 0.36; 95% CI 0.17 to 0.75).

The Subcommittee noted the findings of a French Pompe Registry data which included 12 patients with severe respiratory failure and permanent wheelchair use at the time of ERT initiation (Papadopoulos C et al. Mol Genet Metab 2017;122:80-5). The Subcommittee noted that during the observational period no adverse reaction to ERT was recorded; five patients (41.67%) died; three decreased their ventilation time by 30, 60 and 90 min, respectively; and two increased their assisted walking distance by 80 and 20 metres, respectively. The Subcommittee considered that the use of ERT in the late stages of LOPD would provide very limited benefit.

Members noted a recent Dutch study investigating the cost-effectiveness of ERT compared to supportive treatment in adult patients with Pompe disease (Kanters et al. Orphanet J Rare Diseases 2017;12:179-91). The Subcommittee noted that the cost-effectiveness model reported substantial survival gains from ERT; and that despite these substantial gains, ERT was not cost-effective in the treatment of adult Pompe disease because of the high cost of treatment.

While recognising the challenges of generating high-quality data for rare conditions such as Pompe disease, the Subcommittee considered that the observational data set for LOPD did not provide a sufficient basis to demonstrate substantial life extension

and there remains significant uncertainty regarding treatment effect. Members considered the clinical benefits with regards to ambulation and pulmonary function are modest.

The Subcommittee noted the high proposed cost of alglucosidase alfa and considered that with uncertain benefits, the cost effectiveness of ERT for all patients with LOPD is very poor.

The Subcommittee noted that they would be interested in considering a re-submission from the supplier for alglucosidase alfa targeted to a sub-group of patients with LOPD in younger patients who could be considered to have juvenile-onset Pompe disease, as it considered this group would likely gain more benefit from treatment. Members noted there are currently no patients in New Zealand who would meet this definition.

The Subcommittee noted there were several new treatments in the development pipeline that may provide alternative treatments to consider in the future.

Publication of minutes

This minute may be made publicly available by publication on our website (www.PHARMAC.govt.nz) or by release following receipt of a request from interested parties. If you consider that any specific content of this minute should be withheld, please notify me in writing by **8 February 2019**. In deciding whether to withhold any sections of this minute from public release, we will follow the rules for withholding information specified in the Official Information Act 1982 (which are enclosed).

Please note that your comments in relation to the public release of this minute would not prevent you from commenting on it or providing further information for consideration by PHARMAC at a later date.

Application status

This minute will be reviewed by PTAC at its February 2019 meeting. PTAC may endorse the Rare Disorder Subcommittee's recommendations or make its own (different) recommendation. Following PTAC's review, further analysis may be conducted by PHARMAC regarding the cost effectiveness and budget impact of funding alglucosidase alfa.

Following your review of this minute you may wish to amend your application or commercial proposal and resubmit to PHARMAC with further comment or information to be considered. PHARMAC may then seek further advice from PTAC or a PTAC Subcommittee.

We appreciate that this is not the outcome that New Zealand patients with LOPD and Sanofi Genzyme were hoping for. As previously discussed, we request that Sanofi Genzyme treats this minute as confidential at this time and does not share the outcome of the Subcommittee review with anyone until the minute is ready to the published on the PHARMAC website. Following your confirmation of any specific content to withhold, PHARMAC staff wish to directly engage with the relevant patients and stakeholders regarding the outcome of the Subcommittee review prior to publishing the minute. We expect this to occur in early February and we will keep you updated on timing regarding this.

We note that the Subcommittee would welcome an application for alglucosidase alfa targeting treatment to those individuals considered to have juvenile-onset Pompe disease. We look forward to discussing this further with you.

Following clinical advice and completion of our assessment processes, including prioritisation, PHARMAC will then determine the next appropriate steps for the applications for rare disorders considered at the meeting, such as possible commercial processes.

If you have any questions, please contact me on [redacted] or by email [redacted]

Yours sincerely

[redacted]

[redacted]

[redacted]

[redacted]