NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Avalglucosidase alfa for treating Pompe disease

1 Recommendations

1.1 Avalglucosidase alfa (AVAL) is recommended, within its marketing authorisation, as an option for treating Pompe disease in babies, children, young people and adults, only if the company provides AVAL according to the commercial arrangement (see section 2).

Why the committee made this recommendation

Pompe disease either occurs at birth (infantile onset; IOPD), or after 12 months (late onset; LOPD). The only treatment for Pompe disease is enzyme replacement therapy (ERT) with alglucosidase alfa (ALGLU). AVAL is an alternative ERT that works in the same way. Limited evidence shows AVAL can enter cells more easily, so reducing glycogen levels more efficiently than ALGLU. But the clinical benefit is uncertain.

In LOPD, the cost-effectiveness estimates are uncertain because of uncertainties in the clinical evidence. But they are below what NICE normally considers an acceptable use of NHS resources, so AVAL is recommended for LOPD.

Because IOPD is very rare, data is limited. So assumptions about its efficacy were needed, which makes the cost-effectiveness estimates uncertain. When assuming that AVAL works as well as ALGLU, cost-effectiveness estimates are below what NICE normally considers an acceptable use of NHS resources. Given the high burden of Pompe disease on children and their carers, and the rarity of the condition, the committee accepted the uncertainties. So AVAL is recommended for IOPD.

2 Information about avalglucosidase alfa

Marketing authorisation indication

2.1 Avalglucosidase alfa (AVAL; Nexviadyme, Sanofi Genzyme) is indicated 'for long-term enzyme replacement therapy for the treatment of Pompe disease (acid alpha-glucosidase deficiency).'

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for AVAL.

Price

2.3 The list price of a 100 mg vial of AVAL is commercial in confidence and cannot be reported here. The product is not commercially available at the time of publication of this final appraisal document.

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes AVAL available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Sanofi Genzyme, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Pompe disease is a rare genetic condition which is severely debilitating, affecting quality of life

3.1 Pompe disease is a rare, genetic, chronic and progressive metabolic disease, resulting in severe disability and a reduced life expectancy.

Pompe disease is caused by mutations in the gene that encodes the enzyme acid alpha-glucosidase (GAA), which is needed to break down glycogen into glucose. In Pompe disease, there is reduced or absent activity of GAA, which causes an accumulation of lysosomal glycogen in muscle cells resulting in irreversible muscle damage. Disease severity is influenced by the level of residual GAA activity. There is a range of phenotypes of Pompe disease, differing in age of onset, extent of organ involvement and rate of progression, which can be classified into 2 broad subtypes: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD). IOPD presents in the first 12 months of life and is typically associated with cardiomyopathy, hypotonia and respiratory distress. If untreated, children will typically need ventilation by 6 months. Clinical experts stated that, in the absence of treatment, they would expect most children with IOPD to have a life expectancy of around 14 months because of heart complications. For LOPD, symptom onset is after 12 months and can happen any time up to late adulthood. LOPD typically affects multiple systems and is characterised by progressive muscle weakness and respiratory involvement. As the disease progresses, people with LOPD may need to use a wheelchair and need non-invasive or invasive ventilation, with respiratory failure being the leading cause of death. There is significant heterogeneity within people with LOPD, including time of symptom onset, time of diagnosis, symptom severity, rate of disease decline and life expectancy. The committee concluded that Pompe disease has a severe effect on both quality and length of life.

Treatment pathway

There are limited treatment options for people with Pompe disease

3.2 Currently, the only treatment option for Pompe disease is alglucosidase alfa (ALGLU), an enzyme replacement therapy (ERT) that has not previously been assessed by NICE. Alongside ALGLU, people with Pompe disease need tailored supportive care from multidisciplinary teams

of health professionals. Response to ALGLU can vary between people. There is a well-recognised need to provide better options for people whose disease is not well managed or if the treatment effect has waned. Patient experts explained how symptom-relieving supportive care interventions can help but also come with additional disadvantages. The committee concluded that there is a need for more effective treatments for Pompe disease.

The availability of avalglucosidase alfa would be expected to provide benefits for people with IOPD and LOPD

3.3 Avalglucosidase alfa (AVAL) is indicated for the long-term treatment of Pompe disease. AVAL is expected to provide benefits as a treatment option for IOPD and LOPD. Clinical experts explained that AVAL is the same enzyme as ALGLU but has a better delivery mechanism which should get more enzyme into muscle cells. Therefore, they expect AVAL to have a positive effect for people with Pompe disease and be a better option than ALGLU. People with Pompe disease are optimistic about future treatment with AVAL. One person who has had treatment with AVAL told of the positive effect it has had on their life. Since treatment with AVAL in the clinical trial, they no longer have mobility or breathing problems, and do not have to worry about not being able to do things that people without the disease may be able to do. The committee concluded that clinicians and people with Pompe disease would welcome an effective alternative to current treatment.

Clinical evidence

Clinical evidence is limited to 2 studies in the LOPD population

3.4 Clinical data is limited in Pompe disease. The key clinical evidence comes from the COMET study and NEO1/NEO-EXT. COMET was a randomised, multicentre, double-blind, active-controlled 49-week study comparing AVAL (n=51) with ALGLU (n=49) in people with LOPD who have not had ERT previously. COMET was a non-inferiority study, aiming to test

whether AVAL is no less effective than ALGLU. The primary outcome in COMET was mean percentage change in forced vital capacity (FVC%), and key secondary outcomes included the six-minute walk test (6MWT), safety and health-related quality of life. NEO1/NEO-EXT was an open-label, multicentre, ascending dose study which assessed the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of AVAL (n=24) and long-term extension (up to week 312; n=19). The primary outcome from NEO1/NEO-EXT was safety and tolerability of AVAL over different doses. NEO1/NEO-EXT also collected change from baseline in FVC% and 6MWT. The committee concluded that the evidence was limited, but acceptable for decision making.

COMET reported no statistically significant benefits in LOPD, although FVC% and 6MWT did improve

3.5 The COMET primary analysis at week 49 showed that AVAL was non-inferior to ALGLU in the FVC% and 6MWT outcome measures. There were some minor positive changes, but these were not statistically significant. AVAL showed a numerical improvement in FVC% from baseline, but this was not statistically significantly better than with ALGLU. There was also a numerical improvement in 6MWT with AVAL, but the statistical significance of this change compared with ALGLU was not reported. Health-related quality of life data collected in COMET showed utility values were generally higher over time than at baseline for both treatments. COMET safety data suggests AVAL and ALGLU are similarly tolerated. The most common adverse events were headache, nasopharyngitis, back pain, fatigue, diarrhoea, and nausea. The committee and clinical experts noted that COMET is a non-inferiority study. The committee accepted that there was nothing to suggest that AVAL was inferior to the current treatment and that there is a theoretical potential for additional benefit.

There appeared to be stability in treatment effect over time in NEO1/NEO-EXT, but data should be interpreted with caution

3.6 Longer-term AVAL clinical data from NEO1/NEO-EXT showed that FVC% and 6MWT results were generally stable over time, although patient numbers in NEO1/NEO-EXT were small. The committee and clinical experts would have expected to see an improvement in FVC% and 6MWT after week 49 when people who were initially having ALGLU switched to AVAL, if AVAL was a more effective treatment, but this was not apparent in the data. Clinical experts explained that sometimes a maintenance of effect is a positive sign of slowing a progressive disease such as LOPD. The committee concluded that caution should be taken when interpreting long-term NEO1/NEO-EXT data.

Data for the IOPD population comes from mini-COMET and is uncertain because of heterogeneity, small sample sizes and limited follow up

3.7 Clinical data was very limited in the IOPD population. Clinical evidence for AVAL in the IOPD population came from a multi-stage, open-label, multicentre, ascending dose study including 3 cohorts (mini-COMET). Only cohort 3 compared AVAL with ALGLU. Children in mini-COMET had previously had ALGLU. There is no data for children with IOPD who have not previously had ERT. Cohort 1 and Cohort 2 included children with clinical decline, Cohort 1 had AVAL 20 mg/kg every 2 weeks and Cohort 2 had AVAL 40 mg/kg every 2 weeks. Cohort 3 was the randomised portion of the trial, with children having either AVAL at the highest tolerated dose (n=5) or ALGLU at the current stable dose (n=6). Mini-COMET enrolled 22 people (Cohort 1, n=6; Cohort 2, n=5; Cohort 3, n=11). Therefore, comparative data is only available from 11 children, all of whom had a suboptimal disease response to ALGLU. Clinical experts explained that for the purposes of the study, children were divided into groups classified as suboptimal response, or clinical decline, but the classification would depend on which outcome measure was used. There was also variation in the doses given. Some children had weekly treatment, and some had doses greater than currently used in NHS clinical practice. Clinical experts

explained current practice is to offer ALGLU weekly 20 mg/kg at the start of treatment, at least for the first 12 weeks. They stated that evidence was emerging that a dose of 40 mg/kg ALGLU is more effective than 20 mg/kg. Clinical experts would expect any dose increase for ALGLU to also apply to AVAL. The committee was aware that it could only recommend any treatment in line with its marketing authorisation. Clinical experts considered the efficacy data from mini-COMET to be too heterogeneous and uncertain to be reliable, but the safety and pharmacokinetic data is satisfactory. Mini-COMET suggests AVAL and ALGLU are similarly tolerated. The committee concluded that the data on IOPD is very limited and uncertain but noted the rarity of the condition makes data collection difficult.

Economic model

The company LOPD simulation model is appropriate for decision making

3.8 The company LOPD model used a simulation approach with 6 health states. Each health state is associated with different costs, quality of life and mortality risks. The company included 8 profiles to model the population that would be likely to have treatment for LOPD in the UK. The profiles were informed by COMET patient-level data and were split by sex, age, time since diagnosis, weight, FVC%, 6MWT and utility. People entered the model not dependent on ventilators or wheelchairs. COMET changes in FVC% informed transitions through ventilator- or invasive ventilator-dependent health states and changes in 6MWT informed transitions through wheelchair-dependent health states. The duration of disease response was informed by NEO-EXT, after which benefits declined at a constant rate. The ERG thought the model health states captured the key aspects and progressive nature of the disease, and the simulation approach captured heterogeneity and patient history. However, the ERG thought that the profiles used by the company included less severely affected people than would typically be seen in NHS practice. Clinical experts would expect AVAL to slow the rate of clinical decline

more than ALGLU. The committee concluded the structure of the model was appropriate for decision making.

The committee accepted that a survival benefit for AVAL was possible, and should be explored

3.9 Overall survival was informed by general population life tables, with hazard ratios (HRs) applied to adjust survival for people with LOPD. The company originally assumed people with LOPD who had AVAL and ALGLU had the same survival prospects. The ERG disagreed, and suggested AVAL should be associated with a survival benefit because of the expected clinical benefits associated with AVAL treatment. The ERG suggested that a HR of 0.85 should be applied to AVAL overall survival which translated into a 3-month survival gain for people who had AVAL. The company accepted this HR approach and included it in the base-case analysis. Clinical experts stated that a survival benefit for people who had AVAL was possible but noted that there is no survival data to confirm or quantify this. The committee concluded that a survival benefit for AVAL over ALGLU was plausible, but unproven. It accepted that it was reasonable to explore the effect of an assumption of improved survival on cost effectiveness.

The company IOPD 4-state partitioned survival model was appropriate, but needed assumptions in place of informative data

3.10 The company IOPD model followed a partitioned survival model approach with 4 health states. People could be ventilation free, dependent on non-invasive ventilation, dependent on invasive ventilation or deceased. Overall survival, ventilator-free survival and invasive ventilator-free survival curves from Broomfield (a case-note review of 33 children who had previously had ALGLU) were extrapolated and formed the basis of the 4-state partitioned survival model. Wheelchair dependence was captured separately to the core health states. The ERG accepted the approach chosen, indicating that the 4 health states captured disease progression, but noted the overall survival curve may not capture risk of

death for children needing artificial ventilation. The committee highlighted that while data is limited for this population, the modelling approach used was appropriate.

Equivalent survival outcomes were an area of uncertainty in the IOPD model

3.11 Mini-COMET has short follow up and small patient numbers, so relative effectiveness is uncertain. In the absence of long-term survival data from trials in children with IOPD, the company used published data from the Broomfield case-note study of children who had ALGLU. The company assumed disease progression and survival prospects for children who had AVAL would be the same as seen in Broomfield (assuming equivalence). The ERG agreed that mini-COMET data is too limited to inform survival, or to confirm or reject equivalence. The ERG ultimately accepted the company's approach of equivalent survival but ran scenario analyses with a survival advantage for children who had AVAL. In these scenarios, children live longer and have treatment for longer, resulting in substantially higher incremental cost-effectiveness ratios (ICERs). Clinical experts suggested that it is plausible that children who had AVAL could have a survival advantage. However, they explained any benefit would also bring other benefits such as slower progression and better quality of life which has not been modelled in the scenarios. The ERG accepted the scenarios are an oversimplification of a complex progressive disease, but highlighted limitations of available IOPD data. The committee concluded that they were satisfied with equivalence assumptions in the IOPD population but accepted the uncertainty.

Cost-effectiveness estimates

AVAL is likely to be cost effective in LOPD

3.12 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective

use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The company's and ERG's cost-effectiveness estimates for AVAL in people with LOPD were well below what NICE normally considers an acceptable use of NHS resources. The company's and ERG's base-case analyses differed only in the duration of response for ALGLU and AVAL. The company assumed a greater duration of response for AVAL, whereas the ERG assumed an equivalent duration for both treatments. Even when considering this change, AVAL would still be a dominant use of NHS resources when compared with ALGLU (that is, it costs less and is more effective). The committee concluded that AVAL would be a cost-effective treatment option for LOPD, so it is recommended.

AVAL is also likely to be cost effective in IOPD, although results are more uncertain

3.13 The company's and ERG's base-case cost-effectiveness estimates for AVAL in children with IOPD were also well below what NICE normally considers an acceptable use of NHS resources. The company's and ERG's base-case analyses differed in dosing, survival extrapolation and utility assumptions, but even when considering these changes, AVAL would still be a dominant use of NHS resources. Scenario analyses done by the ERG investigating survival gains for children who had AVAL saw ICERs increase to values not considered cost effective. The committee noted these scenarios were exploratory and informed by assumptions and not survival data. The committee would have preferred to have seen a full cost-utility analysis in IOPD, informed by robust comparative clinical data but acknowledged that, in this specific case, this was not available. However, given current limited IOPD evidence suggesting that AVAL is non-inferior to ALGLU, the high burden of Pompe disease on children and their carers, and the rarity of the condition, the committee accepted uncertainties in dosing, overall survival and duration of response in IOPD.

The committee concluded that AVAL is likely to be a cost-effective treatment option for IOPD, so it is recommended.

Innovation

3.14 AVAL is anticipated to address the unmet need of a population of people with Pompe disease for whom existing treatment is suboptimal. Clinical experts explained that AVAL is a second-generation ERT, and that alterations made to the GAA enzyme are designed to improve the efficiency of the uptake of the enzyme rather than being a step change in management. The company argued that AVAL is quicker to reconstitute than ALGLU which could reduce vial preparation time and free up capacity in the NHS. The committee concluded that all additional benefits of AVAL had already been taken into account.

Conclusion

3.15 AVAL is recommended for use in the NHS for treating Pompe disease. The cost-effectiveness estimates for both IOPD and LOPD were uncertain. But they were likely to remain below what is considered an acceptable use of NHS resources even when accounting for the uncertainty.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Because avalglucosidase alfa (AVAL) has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication or commercial availability of the product.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has Pompe disease and the doctor responsible for their care thinks that AVAL is the right treatment, it should be available for use, in line with NICE's recommendations.

Jane Adam
Chair, appraisal committee
July 2022

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Lewis Ralph
Technical lead

Michelle Green
Technical adviser

Thomas Feist
Project manager

ISBN: [to be added at publication]