CLINICAL PRIORITIES ADVISORY GROUP
18 July 2022

Agenda Item No	4.1
National Programme	Women and Children
Clinical Reference Group	Metabolic
URN	2107

Title
Alglucosidase alfa for patients with infantile-onset Pompe disease (all ages) 2107

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
Pompe disease is a very rare disease which causes damage to muscles and can lead to mobility difficulty, breathing problems and death before two years in untreated patients. Infantile-onset Pompe disease is when the symptoms start in children under one year old and affects the heart muscle as well as the muscles of movement and breathing. Patients with infantile-onset Pompe disease can be treated with a medication called alglucosidase alfa, which replaces the enzyme that may be missing or not working properly. Alglucosidase alfa is given as a regular injection into a vein. The proposed treatment is to use the same medication but at an increased frequency (once every week instead of once every two weeks) and/or at an increased dose. There is evidence that this increase in the dose improves outcomes for patients, there is significant morbidity and mortality associated with this variant pf Pompe disease. There are 17 patients in treatment in England with infantile onset Pompe Disease currently that would be expected to be treated under this policy and it is expected that 3 new patients will present annually.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Outcome 1 **Survival** **Certainty of evidence:** Very low	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Without treatment, life expectancy is less than 2 years and even with current treatment, survival is not guaranteed. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to survival at the end of the study. It compared outcomes in infants newly diagnosed with IOPD who were treated with

	alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. At the end of the study, the difference between the groups was not statistically significant for this outcome. 11/12 (92%) patients survived in the 40 mg/kg group compared with 4/6 (67%) patients in the 20 mg/kg group (p=0.25). **(VERY LOW)** Dosages were increased to 40 mg/kg once weekly in 4 surviving patients (median age 4.1 years) receiving 20 mg/kg once every 2 weeks because of clinical deterioration. It is possible that this dosage increase caused the difference between the groups to be less than it would have been if they had remained on 20 mg/kg once every 2 weeks. **This study provides very low certainty evidence of no difference in the proportion of people surviving when alglucosidase alfa 40 mg/kg once weekly is compared with the licensed dosage. However, this result might underestimate a survival benefit for the 40 mg/kg once weekly group.**
Survival **Certainty of evidence:** Very low	Study published online (Ditters et al. 2021), providing new evidence that substantively supports the higher dosage of 40mg/kg once a week (compared to 20 mg/kg every other week). This paper was not included in the final evidence review. Main findings: Patients with classic infantile Pompe disease treated with the high ERT dosage of 40 mg/kg per week had significantly improved survival when compared with patients treated with the standard recommended ERT dosage of 20 mg/kg every other week (hazard ratio [HR] 0·17 [95% CI 0·04–0·76], p=0·02). **This study provides very low certainty evidence of no difference in the proportion of people surviving when alglucosidase alfa 40 mg/kg once weekly is compared with the licensed dosage. However, this result might underestimate a survival benefit for the 40 mg/kg once weekly group.**

Outcome 2 **Ventilation free survival** **Certainty of evidence:** **Very low**	This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Without treatment, life expectancy is less than 2 years and even with current treatment, survival is not guaranteed. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to survival at the end of the study. It compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. At the end of the study, the difference between the groups was not statistically significant for this outcome. 11/12 (92%) patients survived in the 40 mg/kg group compared with 4/6 (67%) patients in the 20 mg/kg group (p=0.25). (VERY LOW) Dosages were increased to 40 mg/kg once weekly in 4 surviving patients (median age 4.1 years) receiving 20 mg/kg once every 2 weeks because of clinical deterioration. It is possible that this dosage increase caused the difference between the groups to be less than it would have been if they had remained on 20 mg/kg once every 2 weeks. **This study provides very low certainty evidence of no difference in the proportion of people surviving when alglucosidase alfa 40 mg/kg once weekly is compared with the licensed dosage. However, this result might underestimate a survival benefit for the 40 mg/kg once weekly group.**
Outcome 3 **Health related quality of life** **Certainty of evidence:** **Not applicable**	Quality of life is very important to patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived well-being. No evidence was identified for this outcome.
Important outcomes	
Outcome 4 **Rate of gastrostomy/jejunostomy placement** **Certainty of evidence:** **Very low**	Patients with IOPD may require gastrostomy or jejunostomy placement because of difficulty swallowing. This impedes the patient's ability to eat and drink normally and requires training for the carers to use. A reduction in gastrostomy/jejunostomy placement would be very important to patients.

	One before and after study (Poelman et al. 2020, n=18) provided evidence relating to gastrostomy placement at the end of the study. It compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. Few patients in the study had gastrostomy placement. At the end of the study, 1/12 (8%) patients in the 40 mg/kg group had received percutaneous endoscopic gastrostomy compared with 2/6 (33%) patients in the 20 mg/kg group. No statistical analysis was reported for this outcome. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. (VERY LOW) **This study provides very low certainty evidence and it is unclear whether alglucosidase alfa 40 mg/kg once weekly reduces gastrostomy placement compared with the licensed dosage.**
Outcome 5 **Motor Function** **Certainty of evidence:** **Low to very low**	The ability for patients to meet motor milestones (including crawling and walking) are important to patients and carers as they are a marker of the development of the brain. This is an important outcome to patients as resolution or reduction of these disease-related complications can reduce the number of times they need to be admitted to hospital or require emergency admissions. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to motor function at various timepoints throughout the study. The study assessed ability to walk and AIMS and BSID-II scores in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Ability to walk Overall, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly achieved walking outcomes compared with patients using the licensed dosage. However, the difference was only

	reported to be statistically significant for ability to walk at 3 years and results for the other outcomes are unclear. • The ability to walk was achieved by 11/12 (92%) patients in the 40 mg/kg group and 4/6 (67%) patients in the 20 mg/kg group (no statistical analysis reported). (VERY LOW) • At the age of 3 years, 11/12 (92%) patients in the 40 mg/kg group maintained the ability to walk compared with 2/6 (33%) patients in the 20 mg/kg group (p=0.02). (LOW) • At the end of the study, 10/12 (83%) patients in the 40 mg/kg group maintained the ability to walk compared with 1/6 (17%) patients in the 20 mg/kg group (no statistical analysis reported). (VERY LOW)
Outcome 6 **AIMS scores** **Certainty of evidence:** **Low to very low**	AIMS is a 58-item scale on which lower scores indicate delayed development. This scale was used to assess motor development when infants were aged 12 months 12 and 18 months. The scale has not been validated for use in Pompe disease and there is no known standard minimal clinically important difference. Median AIMS scores and ranges were similar between the groups, although no statistical analyses were reported. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. • At 12 months, the median AIMS score was 39 (range 20-50) in the 40 mg/kg group and 37 (range 20-45) in the 20 mg/kg group (5 patients only because 1 had died). (VERY LOW) • At 18 months, the median AIMS score was 57 (range 34-58) in the 40 mg/kg group and 54 (range 25-57) in the 20 mg/kg group (5 patients only because 1 had died). (VERY LOW) Only 6 patients reached the maximum AIMS score of 58 and all were in the in the 40 mg/kg group. BSID-II scores BSID-II consists of 3 scales (motor, mental and behaviour) with a score of 100 being average for age, and lower scores indicating delayed development. This scale was used to assess motor development when infants were aged 24 months and 36 months. The scale has not been validated for use in Pompe disease and there is no known standard minimal clinically important difference. Median BSID-II scores and ranges were generally similar between the groups, although no statistical analyses were reported. The study authors reported that statistical analyses could only be applied for a limited number

	of outcome measures because of the small sample sizes. At 24 months, the median BSID-II score was 18 (range 14-25) in the 40 mg/kg group and 17 (range 10.4-21) in the 20 mg/kg group (3 patients only because 1 had died and 2 needed invasive ventilation). (VERY LOW) At 36 months, the median BSID-II score was 30 (range 19-33) in the 40 mg/kg group (11 patients only because 1 had died) and 20 (range 20-32) in the 20 mg/kg group (3 patients only because 1 had died and 2 needed invasive ventilation). (VERY LOW) **This study provides low certainty evidence that, compared with patients using the licensed dosage, more patients using alglucosidase alfa 40 mg/kg once weekly are still able to walk at 3 years and very low certainty evidence that more patients achieved the ability to walk and were still able to walk at the end of the study.** **The study provides very low certainty evidence that median AIMS and BSID-II scores and ranges were generally similar in the alglucosidase alfa 40 mg/kg group and the licensed dosage group**
Outcome 7 **Disease related complications** **Certainty of evidence: Very Low**	Resolution of disease-related complications (such as clinically significant cardiomyopathy) is an important outcome to patients as resolution or reduction of such complications can reduce the number of times they need to be admitted to hospital or require emergency admissions. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to resolution of disease-related complications. It assessed LVMI at the end of the study, which is a measure of cardiomyopathy, a complication related to Pompe disease. The study compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. The results of the study were presented graphically for this outcome. Changes in LVMI Z-scores appeared to be similar between the groups and generally improved, but no statistical analyses were reported. (VERY LOW) The study authors reported that statistical analyses could only be

	applied for a limited number of outcome measures because of the small sample sizes. LVMI did not normalise in 1 patient in the 20 mg/kg group who died after 3 months of treatment. 2 patients in the 40 mg/kg group had severe cardiomyopathy at baseline, which responded well to treatment, although LVMI was still slightly elevated at the last assessment in 1 patient. **This study provides very low certainty evidence and it is not known whether alglucosidase alfa 40 mg/kg once weekly improves LVMI compared with using the licensed dosage.**
Safety	
Outcome 1 **Drug-related adverse events** **Certainty of evidence:** **Not applicable**	Drug-related adverse events (side effects) are important to patients because they will impact on their treatment choices and recovery and can sometimes have longterm consequences. No evidence was identified for this outcome.
Outcome 2 **Infusion-associated reactions** **Certainty of evidence:** **Very low**	Infusion-associated reactions are important to patients because they can be very unpleasant and sometimes severe or life threatening. Also, they can occur repeatedly with subsequent infusions. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to infusion-associated reactions during the study. It compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. Overall, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly had infusion-associated reactions compared with patients using the licensed dosage. However, no statistical analyses were reported. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. 8/12 (67%) patients in the 40 mg/kg group experienced infusion-associated reactions compared with 5/6 (83%) patients in the 20 mg/kg group. (VERY LOW) 134 infusion-associated reactions (11 severe) were seen in the 40 mg/kg group compared with 64

	reactions (4 severe) in the 20 mg/kg group. (VERY LOW) In all but 2 patients, reactions were treated successfully and had not recurred for at least 12 months. **This study provides very low certainty evidence suggesting that more infusion-related reactions are seen with alglucosidase alfa 40 mg/kg once weekly compared with the licensed dosage of alglucosidase alfa.**
Outcome 3 **Antibody formation and detection** **Certainty of evidence: Very low**	Patients can develop antibodies to alglucosidase alfa. This is important to them because high titres (concentrations) of antibodies are associated with worse outcomes (including adverse events), especially if they are sustained for a long period. Overall, patients using alglucosidase alfa 40 mg/kg once weekly had higher antibody titres than patients using the licensed dosage. However, no statistical analyses were reported. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. The median peak antibody titre was 1:156,250 (range 1:250 to 1:800,000) in the 40 mg/kg group and 1:6250 (range 1:1250 to 1:31,250) in the 20 mg/kg group. (VERY LOW) 2/6 (33%) patients in the 20 mg/kg group and 7/12 (58%) patients in the 40 mg/kg group developed high sustained titres of 1:31,500 or more. (VERY LOW) This study suggests that higher antibody titres are seen with alglucosidase alfa 40 mg/kg once weekly compared with the licensed dosage of alglucosidase alfa. However, this evidence is of very low certainty.

In the Population what is the cost effectiveness of the Intervention compared with Comparator?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified regarding the cost-effectiveness of alglucosidase alfa 20-40 mg/kg once weekly for IOPD.

From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

Outcome Subgroup: CRIM status	Patients whose bodies do not produce any alfa glucosidase enzyme are known as CRIM-negative. Patients who are CRIM-positive produce a small amount of the enzyme, but it is inactive. CRIM-negative patients produce more antibodies to treatment and have been shown to have worse outcomes. Outcomes in CRIMpositive patients are variable. (Poelman et al. 2020) In the study by Poelman et al. (2020), 5/18 (28%) patients were CRIM-negative, 3/12 (25%) in the 40 mg/kg group and 2/6 (33%) in the 20 mg/kg group. All 3 CRIM-negative patients in the 40 mg/kg group survived, whereas the 2 in the 20 mg/kg group died. 2/3 patients in the 40 mg/kg group also received immunomodulation treatment (in another arm of the study), which may have influenced their outcomes, although the study concluded that immunomodulation did not prevent antibody formation in the 40 mg/kg group compared with the 20 mg/kg group. When considering motor scores, 2/3 patients in the 40 mg/kg group who were CRIM-negative reached the maximum AIMS score of 58. No patients in the 20 mg/kg group reached this score, regardless of CRIM status. All 3 CRIM-negative patients in the 40 mg/kg group developed high sustained antibody titres whether they received immunomodulation or not, as did 1 of the 2 CRIM-negative patients in the 20 mg/kg group. One CRIM-positive patient died, who was in the 40 mg/kg group. All 3 CRIMpositive patients in the 20 mg/kg group and 4/9 (44%) CRIM-positive patients in the 40 mg/kg group (including 1 also received immunomodulation) developed high sustained antibody titres. CRIM status was not a prespecified subgroup in the study, the number of CRIMnegative patients was very small and no statistical analyses were presented for these outcomes. **The study suggests that CRIM-negative patients taking alglucosidase alfa 40 mg/kg weekly may live longer and have better motor function than those taking the licensed dosage. However, this evidence is inconclusive. Less information was reported for CRIM-positive patients and the benefits and risks with 40 mg/kg compared with 20 mg/kg are not known for this subgroup**

From the evidence selected, when do patients change dose of enzyme replacement therapy?

Outcome	Evidence statement
Change of dosage	In the study by Poelman et al. (2020), 6 patients with IOPD received alglucosidase alfa 20 mg/kg once every 2 weeks

	between 2003 and 2009. From 2009, all patients received 40 mg/kg once weekly. Between 2009 and 2014, dosages were increased to 40 mg/kg once weekly in the 4 surviving patients receiving 20 mg/kg once every 2 weeks because of clinical deterioration. Their median age was 4.1 years (range 1.5 to 9.4 years) at the time of the increase. No further information is reported. Dosages were increased in patients taking 20 mg/kg once every 2 weeks when they deteriorated clinically at a mean age of 4.1 years.

Abbreviations	AIMS, Alberta Infant Motor Scale; BSID-II, Bayley Scales of Infant Development II; IOPD, infantile-onset Pompe Disease; LVMI, left ventricular mass index; CRIM, cross-reactive immunological material.

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have severe problems in walking about OR are unable to transfer independently
- **ability to provide self-care:** Patients can have severe problems in washing or dressing OR are unable to wash or dress with significant upper limb involvement
- **undertaking usual activities:** Patients have severe problems in doing their usual activities OR are unable to do their daily activities
- **experience of pain/discomfort:** Patients have pain or discomfort often stemming from the increased risk of fractures of the lower limbs
- **experience of anxiety/depression:** Patients are moderately to extremely anxious or depressed

Further details of impact upon patients:

With maximal current therapeutic intervention 30 % of the UK infantile-onset Pompe disease (IOPD) population die, while only 30% of patients are ambulatory to any extent. Of those surviving more than a year post diagnosis, 30 % require long term invasive ventilation. The musculoskeletal involvement is typical of a myopathy i.e. there is a loss of proximal function which can progress distally with the lower limbs being affected more severely than the arms. There is also the potential for smooth muscle involvement which may result in gastrointestinal dysmotility as well as urinary retention. In the most severe cases patients are quadriplegic, ventilated and fed via gastrostomy utilising eye movements to communicate. These patients are completely dependent on the care of others for all their needs. Given that the intellectual capacity of the patients is normally retained the level of frustration and potential for subsequent depression is high.

Further details of impact upon carers:

IOPD when as severe as detailed above requires 24 hour help i.e. the need to have carers in the family home with the resulting potential loss of privacy. Many parents have given up their work/ limited their working life. While the effects on anxiety, depression as with any heavily dependent child, are well recognised.

Considerations from review by Rare Disease Advisory Group

Pharmaceutical considerations
The policy proposition supports the use of alglucosidase alfa for the treatment of people with infantile-onset Pompe disease. The recommendations are outside the product's marketing authorisation, which is for a dose of 20mg/kg once every two weeks. Alglucosidase alfa is excluded from tariff. A sub-group of metabolic disorders pharmacists has confirmed that they do not have any specific safety concerns regarding the use of alglucosidase at a higher dose/frequency, based on the available evidence, although limited, and clinical experience.

Considerations from review by National Programme of Care
The proposal received the full support of the Women and Children Programme of Care on 7th July 2022