Engagement Report

Topic details

Title of policy or policy statement:	Alglucosidase alfa for patients with infantile-onset Pompe disease (all ages)
Programme of Care:	Women and Children
Clinical Reference Group (CRG):	Metabolic Medicine
URN:	2107

1. Summary

This report summarises the feedback NHS England received from engagement during the development of this policy proposition, and how this feedback has been considered. In total, one feedback form has been received during the stakeholder engagement process, supportive of the policy proposition.

2. Background

Alglucosidase alfa is recommended to be available as a routine commissioning treatment option for patients with infantile-onset Pompe disease (IOPD) within the criteria set out in this document. The policy proposition has been developed by a Policy Working Group (PWG), including a Clinical Lead, a Lead Commissioner, a Public Health Lead.

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.

Patients with IOPD are treated with alglucosidase alfa, which has marketing authorisation for long-term enzyme replacement in patients with confirmed Pompe disease. The marketing authorisation is for the use of 20mg/kg administered intravenously once every two weeks. In England, patients with IOPD currently receive initial treatment of 20mg/kg weekly for the first three months at diagnosis followed by ongoing treatment of 20mg/kg once every two weeks. Some patients develop high titres of anti-drug antibodies related to the administration of enzyme replacement, which is correlated with a poorer outcome.

Proposed treatment

The proposed treatment is alglucosidase alfa at an off-label dose or frequency as described in Table 1.

Table 1: dose of alglucosidase alfa in the different patient populations.

	Current treatment Dose	**Proposed treatment Dose**
Newly diagnosed treatment naïve IOPD patients.	20mg/kg once weekly for three months followed by 20mg/kg once every two weeks.	20mg/kg once weekly alglucosidase alfa
IOPD patients already on enzyme replacement therapy who are not invasively ventilated.	20mg/kg once weekly for three months followed by 20mg/kg once every two weeks.	20mg/kg once weekly alglucosidase alfa
Patients with discernible clinical decline[1], (for example deteriorating respiratory or cardiac function or worsening motor function) despite treatment with 20mg/kg once weekly.	20mg/kg once weekly for three months followed by 20mg/kg once every two weeks.	up to 40mg/kg once weekly alglucosidase alfa

Patients who meet <u>all</u> of the following inclusion criteria can be considered for treatment with alglucosidase alfa at the proposed treatment dose (see Table 1):

1) Diagnosis of infantile-onset Pompe disease (IOPD):
    a) deficiency of endogenous acid alfa-glucosidase.
    b) clinical findings of IOPD including muscular hypotonia and hypertrophic cardiomyopathy.
2) Agreement by a Lysosomal Storage Disease (LSD) multi-disciplinary team (MDT) within a highly specialised service (HSS), that alglucosidase alfa at the specified frequency and dose is the most appropriate treatment option.

Patients who meet <u>any</u> of the following exclusion criteria should not be considered for treatment with alglucosidase alfa:

- Known hypersensitivity to alglucosidase alfa that is clinically unmanageable.
- Newly diagnosed patient already requiring invasive ventilation prior to starting enzyme replacement therapy unless the need for invasive ventilation is due to cardiac failure that could reasonably be expected to improve after treatment initiation

Patients who meet <u>all</u> of the inclusion criteria and <u>none</u> of the exclusion criteria should start or continue treatment with alglucosidase alfa at 20mg/kg once weekly. Patients started on alglucosidase alfa should remain under the care of the LSD MDT within a highly specialised service centre. It is recommended that every patient is reviewed in the LSD centre every 4 months for the first year and subsequent follow-up should be at least every 6 months. The dose may be increased up to 40mg/kg once weekly if there is evidence of discernible clinical decline. Discernible clinical decline may be evidenced by deterioration in three domains:

1) Respiratory Function:

[1] See starting criteria

e.g. development (or worsening) of respiratory failure requiring the use (or increased use) of ventilatory assistance.

2) Motor Skills:
   e.g. failure to acquire and maintain age appropriate gross motor milestones as determined by physiotherapy or neurological assessment, or deterioration of skeletal myopathy.
3) Cardiac Parameters:
   e.g. left ventricular mass (LVM) Z-score ≥ 6 or LVMI ≥ 150 g/m2.

If the decline is not halted or reversed, or no other benefit is noted with the higher dose by 12 months, then dosage should be decreased.
The specialist metabolic MDT should stop treatment with alglucosidase alfa in any of the following circumstances:

- Adverse events (e.g. infusion associated reactions) where harm exceeds the benefit at any time during treatment.
- If an LSD MDT within a highly specialised service centre determine that there are no benefits of continued treatment.

3. Engagement

NHS England has a duty under Section 13Q of the NHS Act 2006 (as amended) to 'make arrangements' to involve the public in commissioning. Full guidance is available in the Statement of Arrangements and Guidance on Patient and Public Participation in Commissioning. In addition, NHS England has a legal duty to promote equality under the Equality Act (2010) and reduce health inequalities under the Health and Social Care Act (2012).

The policy proposition was sent for stakeholder testing for 2 weeks from 28 April 2022 to 12 May 2022. One response has been received. The comment has been shared with the Policy Working Group to enable full consideration of feedback and to support a decision on whether any changes to the proposition might be recommended.

Respondents were asked the following questions:

- Do you support the proposal for alglucosidase alfa to be available as a routine commissioning treatment option for patients with infantile-onset Pompe disease (IOPD) through routine commissioning based on the evidence review and within the criteria set out in this document?
- Do you believe that there is any additional information that we should have considered in the evidence review? If so, please give brief details.
- Do you believe that there are any potential positive and/or negative impacts on patient care as a result of making this treatment option available? If so, please give details.
- Do you have any further comments on the proposition? If Yes, please describe below, in no more than 500 words, any further comments on the proposed changes to the document as part of this initial 'sense check'.
- Please declare any conflict of interests relating to this document or service area.
- Do you support the Equality and Health Inequalities Impact Assessment?

A 13Q assessment has been completed following stakeholder testing. (delete the not applicable paragraphs)

The Programme of Care has decided that the proposition offers a clear and positive impact on patient treatment, by potentially making a new treatment available which widens the range of treatment options without disrupting current care or limiting patient

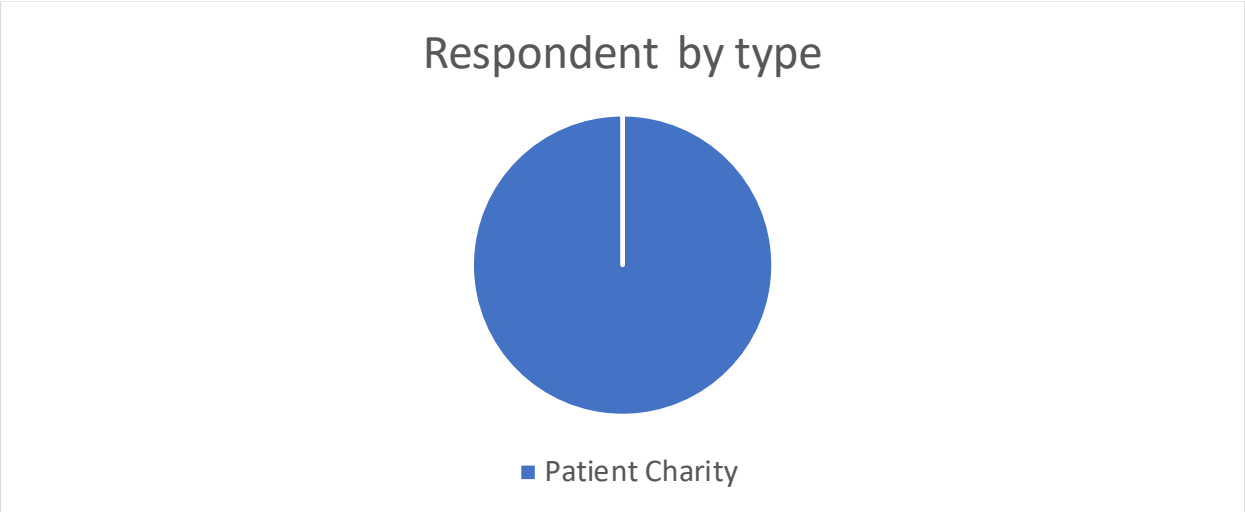
choice, and therefore further public consultation was not required. This decision has been assured by the Patient Public Voice Advisory Group.

Respondents were asked the following consultation questions:

- RC: Do you support the proposition for IOPD for alglucosidase alfa to be available through routine commissioning based on the evidence review and within the criteria set out in this document?
- Do you believe that there is any additional information that we should have considered in the evidence review?
- The impact assessment has been completed to identify the impact of moving from current pathways of care to the one(s) proposed in the draft policy proposition taking into account the anticipated patient numbers, treatment, cost of the treatment and capacity within providers, Do you think that the impact assessment fairly reflects the likely patient numbers, treatment, cost of treatment and the capacity within providers? If not, what do you think is inaccurate?
- The patient pathway describes the patient's journey through the health system to receive current treatment for this condition. Do you think that the policy proposition accurately describes the current patient pathway that patients experience? If not, what is different?
- Please provide any comments that you may have about the potential positive and negative impacts on equality and health inequalities which might arise as a result of the proposed policy that have been described?
- Are there any changes or additions you think need to be made to this document, and why?
- Did you comment on the stakeholder testing for this policy proposition?

4. Engagement Results

In total, one feedback form was received during the stakeholder engagement process 1 from Pompe Support Network (a registered charity).



5. How has feedback been considered?

Responses to engagement have been reviewed by the Policy Working Group and the Woman and Children PoC. The following themes were raised during engagement:

Keys themes in feedback	NHS England Response
Relevant Evidence	
Yes, there are many studies reported from Taiwan and Duke University, USA, that were excluded from the evidence review. In our opinion that was not rational; pooled data from all studies provide very convincing evidence that the higher dosing regimens provide much better outcomes in the real world. The Evidence Review admits that patient numbers were very small, and that proving statistical significance was impossible. However, the benefits can be seen, from global data, to far outweigh the harms from higher dose strategies, so long as the appropriate medical care is given to prevent or treat adverse events. The review should also have considered the effect of age at diagnosis and age at first treatment, because those, as well as CRIM status, have a considerable influence on patient outcomes. We are aware of IOPD children who have responded extremely well after a short period on the Standard of Care, but who have subsequently deteriorated in later life when the treatment was insufficient during periods of greater need (e.g. growth spurts), and patients have lost considerable muscle strength, mobility, dignity and independence. We expect the higher dose to protect many children from such outcomes. The outcomes could be considerably better if infants could be diagnosed through neonatal screening for Pompe disease; but an increased dosing regimen is an important step towards improved outcomes for all IOPD children.	Agree. Only Poelman et al. 2020 was included in the commissioned evidence review. Evidence from Chien et al. 2020 was not included in the review, and Ditters et al. 2021 was published after the review was completed. [Ditters et al. 2021 (observational cohort study n=124) found patients with classic infantile Pompe disease treated with the high dosage of 40 mg/kg per week had significantly improved survival when compared with patients treated with the standard dosage of 20 mg/kg every other week. Chien et al. 2020 (retrospective observational study n=28) found that earlier and higher dosing of alglucosidase alfa improved outcomes in patients with infantile-onset Pompe disease.] These were papers were highlighted in a pharmacy panel convened to review the safety of the higher dosage on 31 January 2022.
Impact Assessment	
We agree with everything contained in the Patient Impact Summary. If anything, we would add further reflections concerning the wide range of patient and carers experiences, as	Agree.

children on the current Standard of Care grow and suffer rapid disease progression during their childhood.	
Current Patient Pathway	
No comments made	
Potential impact on equality and health inequalities	
In the main yes, however we would take issue with the arbitrary age of 12 months at symptom onset to define IOPD for access to the higher dose of alglucosidase alpha. We are concerned that other children could also benefit from the proposed dose increase but will not receive it because their symptoms were not recognised in time. Age of first symptoms is not a precise measurement as it depends on those indicators being recognised by parents and primary care healthcare professionals. In the absence of neonatal screening, early diagnoses are often made by accident. We know that, for example, an enlarged heart and increase in left ventricular mass, may only be identified when the child has an X-ray for a respiratory condition; that then leads to further tests and eventually a confirmed diagnosis of Pompe disease. We are aware of a small number of Pompe patients around the world who received these high doses as juveniles and are still benefitting from them as adults. We would like to see the higher dose available to all children; prescribed at the treating physician's discretion.	The policy has not used explicit age limits in the inclusion or exclusion criteria, specifically to allow the clinician discretion.
Changes/addition to policy	
No comments made in this section	

The responses should answer all the themes reported in section 4 and cover the outcome of reviews of any additional evidence highlighted during engagement

6. Has anything been changed in the policy proposition as a result of the stakeholder testing and consultation?

No

7. Are there any remaining concerns outstanding following the consultation that have not been resolved in the final policy proposition?

No