

Guidance for the Treatment of Late Onset Pompe disease

EDITION No	1
DATE OF ISSUE	15 January 2026
REVIEW INTERVAL	Two years
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Document review history					
Edition No.	Review Date	Reviewed by	Authorised by	Date Authorised	Operative Date
1	November 2025	PPPN	PPPN	January 2025	15 January 2025

Record of Amendments			
Edition No.	Amendment	Amended by & date	Authorised by & date

1.0 First line therapies:

1.1 Enzyme replacement therapy (ERT)

First generation ERT:

- 1) Alglucosidase alfa (Myozyme ®)

Second Generation ERT:

- 1) Avalglucosidase alfa (Nexviadyme ®)
- 2) Cipaglucosidase alfa with miglustat (Pombiliti with Opfolda®), licenced for patients aged 18yrs or older.

2.0 Choice of therapy

ERT:

Formal discussion as to which ERT offers the individual the best possible outcome to be undertaken by specialist prescribing teams. All three therapeutic agents considered first line.

Alglucosidase has been shown to be superior to placebo and the two second generation agents have been shown to be non-inferior to alglucosidase.

3.0 HSCT

Not appropriate

4.0 ERT Dosage

First generation ERT:

- 1) Alglucosidase alfa (Myozyme ®) 20 mg/kg EOW

Second Generation ERT:

- 1) Avalglucosidase alfa (Nexviadyme ®) 20mg/kg EOW
- 2) Cipaglucosidase alfa 20mg/kg EOW with miglustat: for patients weighing ≥ 50 kg, the recommended dose of miglustat is 260 mg (4 capsules of 65 mg). For patients weighing ≥ 40 kg to < 50 kg, the recommended dose is 195 mg (3 capsules of 65 mg) EOW.
(Pombiliti with Opfolda®)

5.0 Patient Group/Diagnosis:

The patient should have a confirmed diagnosis of Pompe disease based on:

- 1) Disease-associated sequence variants on both alleles of the GAA gene or
- 2) Reduced enzyme activity demonstrated by glucosidase alpha enzyme activity testing with and without acarbose inhibition. NB A positive dried blood spot as a first-tier screening test should always be followed by molecular genetic analyses

and/or enzyme activity testing in leukocytes, fibroblasts or other tissues to confirm the diagnosis.

3) Patients need to be eligible for NHS Care.

6.0 Starting Inclusion Criteria

1. The patient should have manifesting clinical disease features with clinically detectable skeletal muscle weakness and/or respiratory muscle involvement assessed on pulmonary function tests.

2. As a supportive paraclinical sign, it is recommended to perform muscle magnetic resonance imaging (MRI) in patients without obvious clinical signs. Muscle MRI demonstrating a fat fraction of 20% or more in at least two muscles is considered as abnormal and indicative for the potential need for disease modifying therapy. (Schooser et al 2024)

3. The patient should have residual skeletal and respiratory muscle function, which is functionally relevant and clinically important for the patient to maintain or improve.

Exclusion Criteria

1. Commencement of ERT is not recommended in patients whose residual functional state is at or worse than:
a) Bedridden state; severe generalized muscle atrophy measured by clinical examination, ultrasound, or muscle MRI;
and b) Minimal residual spontaneous lung function with constant high CO₂ levels, or complete (24 hour or very near 24 hour) dependence on artificial ventilatory support

2. The patient should not have another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate.

MDT treatment approach

Supportive care

Psychology

Palliative

These aspects will be covered by a document in development that will apply across Lysosomal Diseases.

7.0 Investigations at Dx

Baseline Assessment

Patients

Measurement tool

All patients

- Creatine Kinase
 - Vitamin D
 - FBC
 - Renal Profile
 - Molecular Genetics (GAA gene mutation)
 - GAA enzyme activity
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Other Investigations:

Radiology: (Baseline and as clinically indicated)

- 1) Chest Xray or consideration for B-mode ultrasound or fluoroscopy of diaphragm if respiratory compromise
- 2) Optional skeletal MRI (to include thighs, gluteal region and paraspinal muscles) if patient able to lie flat comfortably for 45 minutes.

Cardiology: (Baseline and as clinically indicated)

- 1) Echocardiogram, ECG and 24 hour ECGs baseline and repeat only if clinically indicated.

Neuromuscular

- 1) MRC assessment of muscle function
- 2) 6 minute walk test for ambulant patients
- 3) 10 metre walk test for ambulant patients
- 4) Non ambulatory testing if appropriate, taken from a recognised system such as North Star for Limb-Girdle type Dystrophies (NSAD)

Respiratory: 1. Spirometry: forced vital capacity (FVC) sitting; FVC supine;

2. Sniff Nasal Inspiratory Pressure (SNIP)

3. Polysomnography for those with SNIP < 60cmH₂O or fall in FVC > 20% supine/sitting

4. Assessment of need for ventilatory support by home ventilation experts (if applicable).

Swallowing assessment: At baseline, depending on history of weak phonation, weak cough or suspected risk of aspiration. Repeated as clinically indicated.

8.0 Monitoring:

Urine/ Blood investigations

Patients	Measurement tool	Frequency
All patients	<ul style="list-style-type: none"> • Creatine Kinase • Vitamin D • FBC • Renal profile (Creatinine and electrolytes) • LFTs (as clinically indicated) • Antidrug antibodies if clinically indicated • Consider Urine Hex4 	6-12 monthly

<p>Minimal dataset monitoring assessments required</p> <p>Based on UK consensus</p>	<p>Additional recommended options for monitoring</p>
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Motor function	
Minimal Dataset	Recommended Options

<ul style="list-style-type: none"> • Timed 10-metre walk/run test in all ambulatory patients to capture disease progression and inform use of mobility aids • 6MWT in patients who can safely perform it to facilitate comparison with available clinical trial and retrospective data 	<ul style="list-style-type: none"> • Timed 100-metre walk/run test or timed 10-metre walk/run test should be considered in asymptomatic patients <ul style="list-style-type: none"> – 100-metre walk/run test comprises four laps of a 25-metre course • Muscle MRI should be considered for patients who can comfortably lie flat for 45 minutes <ul style="list-style-type: none"> – Use should depend on expertise of the healthcare team and practical availability of MRI – Muscle MRI can be considered in patients requiring ventilator support if appropriate resources are available
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<ul style="list-style-type: none"> • Appropriate non-ambulatory function tests (e.g. those in the NSAD) for those who cannot perform the timed 10-metre walk/run test • Systematic recording of the use of a wheelchair for patients who are non-ambulatory or can walk less than 10 steps (including number of hours used and location, eg outside/inside home) 	<ul style="list-style-type: none"> – NSAD (North Star Assessment for Limb-girdle Muscular dystrophies) Personnel training may be required for NSAD – NSAD is suitable for assessment of motor function in both ambulant and non-ambulant individuals with LOPD, and includes tasks such as climbing a step, rising from a chair, rising from the floor, sitting up from supine, and mobility
Muscle strength	
Minimal Dataset	Recommended Options
<p>No muscle strength assessments are mandated as part of the minimal dataset</p>	<ul style="list-style-type: none"> • Manual Muscle Testing upper and lower limbs (using MRC scale) should be performed at the discretion of the healthcare team to inform appropriate supportive physiotherapy exercises <ul style="list-style-type: none"> – For example, MMT could be considered in patients with an acute musculoskeletal concern • Measurement of muscle strength using Hand Held Dynamometry should be deprioritized at the discretion of the healthcare team; if limited by available physiotherapy time, functional tests addressing specific movements should be prioritized • Measurement of grip strength using HHD is not recommended as this is affected late in disease progression; difficulty with grip should be evaluated via clinical discussions

Respiratory function	
Minimal Dataset	Recommended Options
<ul style="list-style-type: none"> • Recording ventilation use (yes/no, invasive/non-invasive, overall/daytime number of hours) • SNIP in all patients • Sitting vital capacity in all patients • Sleep assessment for patients with SNIP <60 cm H₂O, sitting to supine drop in FVC of >20%, or clinical symptoms suggesting sleep apnoea or other sleep disturbance 	<ul style="list-style-type: none"> • Supine FVC/FEV1 should be considered if clinically indicated and the patient can lie down without discomfort <ul style="list-style-type: none"> – A handheld device and supine FVC measurement by a trained physiotherapist during motor function testing may be optimal • MIP/MEP should be deprioritized in favour of SNIP <ul style="list-style-type: none"> – For continuity with historical data, the healthcare team may continue MIP/MEP – It is recommended to assess correlation between MIP/MEP and SNIP to determine if SNIP assessment only is sufficient • Peak Cough Flow should be considered when clinically indicated (eg in patients with recurrent chest infections or complaints of difficulty with expiration; PCF of <270 L/min should prompt consideration of a cough assist device) • Daytime blood gas should be assessed if clinically indicated • Impulse oscillometry is not of value.
Patient Reported Outcome Measures	
Minimal Dataset	Recommended Options
<p>One Pompe-specific tool and one general PRO tool are recommended to limit burden on patient/clinician:</p> <ul style="list-style-type: none"> • R-PAct as a Pompe-specific PRO tool in all patients • EQ-5D-5L as a general PRO tool in all patients 	<ul style="list-style-type: none"> • Rotterdam Handicap Scale should be considered if historical data are available to allow continued monitoring • BPI (Brief Pain Inventory) may be considered if clinically indicated • FSS (Fatigue Severity Scale) may be considered if clinically indicated

Other	
Minimal Dataset	Recommended Options
<ul style="list-style-type: none"> • Recording of concomitant conditions • Bone Mineral Density in all patients 	<ul style="list-style-type: none"> • ECG and echocardiogram should be performed in all patients at baseline and subsequently during follow-up if clinically indicated (eg cardiac-related symptoms). • Liver enzymes (AST/ALT) should be performed if clinically indicated • High neutralizing antidrug antibody titres that have resulted in a diminution of the clinical response to ERT can sometimes be detected. It is therefore recommended to investigate high-neutralizing antidrug antibody titres in patients with rapidly declining motor or respiratory function. The cut-off definition of high sustained antibody levels is assay-dependent.
<p>***** There is a lack of validation/ repeatability due to compliance in the paediatric age range for some of the above investigations documented above. Paediatricians managing LOPD patients especially those on therapy, thus may feel the muscular and respiratory outcomes used in the IOPD population are initially more suitable. However, attempts should be made to help establish a data set prior to transition to aid the process.</p>	

9.0 Stopping Criteria (ERT)

Stopping ERT will be discussed with patients and carers and considered in the following circumstances:

1. Intolerable or life-threatening infusion reactions not controllable by standard measures.
2. Inability to perform intravenous cannulation by peripheral or central device.
3. Patient is non-compliant with monitoring regimen preventing ongoing safe administration of therapy. Inter-centre agreement may be helpful. Safeguarding interventions to be explored.
4. Patient develops another life-threatening condition with predicted life expectancy less than 6 months.
5. Patient is no longer eligible for NHS-funded treatment.
6. Patient has declined functionally and there is agreement that treatment is no longer in the patient's best interests.
7. If there is no indication that skeletal muscle function and/or respiratory function have stabilized or improved during the first 2 years after starting or switching treatment, it should be stopped. Inter-centre agreement may be helpful.

9.0 Other cost reducing/saving measures (e.g. vial sharing, procurement etc)

Prescribed dose will be by total body weight unless SPC states otherwise.

For children (< 16 years) ERT dose will be calculated based on body weight and capped at a BMI that is increased +2SD above the median (98th centile) for age.

For adult patients with a BMI of ≥ 27 kg/m² consider capping ERT dose at the dose appropriate for that patient if they had a BMI of 27kg/m².

Vials will be used in integer units, with alternating full-vial dosing as needed, to ensure the most cost-effective use. No drug will be wasted. Where members of the same family are infused simultaneously in the same house the possibility for vial sharing will be explored.

10. Potential impact of stopping drug on patients & other measures needed (e.g. palliative care etc)

For patients stopping drug due to inability to receive intravenous therapy (or due to patient choice not to have therapy), monitoring will proceed as above to monitor rate of disease progression. If, after stopping treatment, the disease deteriorates faster than during treatment, restarting ERT can be considered

For patients ceasing all Pompe specific therapy due to a life-threatening co-morbidity a full evaluation of supportive care requirements will be conducted and delivered in partnership with local primary and secondary care and palliative care teams.

For patients ceasing Pompe-specific therapy due to unexpected supply or compliance issues patients should continue to be monitored by the specialist centre. Cessation of therapy may lead to irreversible progression and thus should there be international shortages of specific ERTs, considerations of changing to alternative ERT should be considered.

Reference

Eur J Neurol 2024 Jun 14;31(9):e16383. doi: [10.1111/ene.16383](https://doi.org/10.1111/ene.16383)
Start, switch and stop (triple-S) criteria for enzyme replacement therapy of late-onset Pompe disease: European Pompe Consortium recommendation update 2024
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