

Guidelines for the treatment of Fabry Disease (see appendix 1 for paediatric disease)

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1.0 First line therapy: Drug Name (generic / commercial)

Agalsidase alfa / Replagal
Agalsidase beta / Fabrazyme
Migalastat / Galafold

2.0 Enzyme replacement therapy (ERT): for adult patients (≥ 16 years) with a confirmed diagnosis of Fabry disease and meeting treatment initiation criteria.

Fabrazyme 1 mg/kg every other week (in some circumstance 0.3 mg/kg eow)
or
Replagal 0.2 mg/kg every other week

3.0 Oral therapy - Migalastat: for adult patients (≥ 16 years) with a confirmed diagnosis of Fabry disease and meeting treatment initiation criteria with a migalastat-amenable mutation.

Migalastat 123 mg every other day at the same time each day.

Comments:

- Not indicated in patients with an eGFR < 30 ml/min.
- As a precautionary measure, it is recommended to avoid the use of Migalastat during pregnancy. This should be discussed prior to commencing therapy.

4.0 Patient Group / Diagnosis

All adult and paediatric patients with a *GLA* gene variant of documented pathogenicity.

Comments:

GLA gene variants of uncertain significance (VUS) in subjects with single organ involvement pose a diagnostic challenge. If the diagnosis remains uncertain, the following may provide supportive evidence of pathogenicity:

- biopsy of the affected organ (e.g. kidney or heart) to demonstrate the characteristic storage pattern by electron microscopy.
- characteristic Fabry cardiomyopathy findings on cardiac magnetic resonance imaging (cMRI)
- plasma lyso-Gb3 levels ≥ 2.7 nM (diagnostic sensitivity and specificity of 100% in patients with “non-classic” *GLA* variants).

Prior to commencing treatment, a full discussion regarding the expected outcomes of therapy and the possibility of treatment discontinuation should the disease continue to progress should be had.

5.0 Starting Criteria:

Comments:

No trial has yet addressed the appropriate starting time of Fabry-specific therapy or the group of patients most likely to benefit from therapy. However, this is a chronic, slowly progressive disorder and the aim of treatment is to delay / reverse progression or stabilise current parameters. It is anticipated that treatment will be most successful when started early in the course of the disease. Treatment late in the course of the disease may have limited efficacy.

In males with “classical variants” (leucocyte enzyme activity <5% and a classical phenotype) Fabry-specific therapy should be considered at diagnosis.

In adult females and males with ‘later onset’ disease, Fabry-specific therapy should commence when one of the following criteria are fulfilled:

5.1 Evidence of Fabry-related renal disease (one of):

- Chronic kidney disease (CKD) stage 3: at least 2 consistent estimates or measured GFR over a minimum of 6 months.
- CKD stage 2: at least 3 consistent estimates or measured GFR over at least 12 months with a GFR slope greater than age-related normal (0.8-1.0 ml/min/year)
- Persistent proteinuria: increased albumin:creatinine or protein:creatinine ratio for males (<https://renal.org/information-resources/the-uk-ekkd-guide/proteinuria/>). Females seldom progress to end stage renal failure (ESRF). In females, if proteinuria is the only presentation – anti-proteinuria medications (ACEi/ARB) should be tried in the first instance for a minimum period of 12 months.

5.2 Evidence of Fabry-related cardiac disease (one of):

- LV wall thickness >13 mm in males and >12 mm in females.
- LV mass index by 2D echo / cMRI above normal for age and sex.
- Late gadolinium enhancement on cMRI.

5.3 General symptoms of Anderson-Fabry disease:

- Uncontrolled pain or gastrointestinal symptoms leading to a need to alter lifestyle or which significantly interferes with quality of life.

Comments:

- Patients whose sole eligibility criterion is gastrointestinal symptoms should have been assessed first by a gastrointestinal team, with a trial of conventional GI therapy.
- Patients whose sole eligibility criterion is pain should have been assessed first by a specialist pain team, with a trial of conventional pain therapy.
- If Fabry related symptoms are the only indication for consideration of Fabry-specific therapy a trial could be given for a year with pre-specified outcomes agreed as to what would constitute a positive effect for symptom control. Such outcomes may include:
 - Reduction in the need for analgesia
 - Reduction in time lost from work
 - Significant Improvements in validated pain scores and / or quality of life measures.

6.0 Exclusion criteria for starting Fabry-specific therapy

- Patients with Fabry disease who are deemed too severely affected to benefit from Fabry-specific therapy (e.g. severely incapacitated following stroke / dementia).
- The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by Fabry-specific therapy.
- End stage renal failure requiring dialysis in the absence of other starting criteria.

7.0 Efficacy measures (with goals)

Biochemical:

- Plasma lysoGb3 concentration (reduction from baseline by 20% after ≥ 12 months of therapy).

Renal:

- eGFR change (decline by < 4 ml/min/1.73m²/year)
- Initiation of renal replacement therapy (no requirement)
- Renal transplant (no requirement)

Cardiac:

- LVMI (gain < 6 gm / m² over the previous 3 year period)
- Cardiac rhythm monitoring (no requirement for therapeutic device insertion)
- Systolic and diastolic function (to prevent dysfunction with worsening of heart failure symptoms).

Other:

- Neurological endpoints (no new TIA / stroke)
- Brief Pain Inventory score (improvement)
- EQ5D Quality of Life score (Improvement)
- Composite clinical endpoint - to include new renal end stage renal disease, arrhythmia requiring pacemaker or defibrillator, stroke or death (improvement)

8.0 Follow-up

With each ERT infusion (unless patients are self-administering enzyme) vital signs and adverse events should be recorded.

Patient receiving Fabry-specific therapy should have at least a 12 monthly review in person at an LSD centre, with an additional review every 6 months (in person, or by telephone as clinically indicated) including the following assessments:

	Baseline	6 Months	Yearly	Every 3-5 Years
General				
Medical history	X	X	X	
Clinical examination	X	X ¹	X	
Family pedigree	X			
Pain score (BPI)	X		X	

QoL score (EQ5D), Fabry Specific	X		X	
Investigations				
ECG	X		X	
24 hour ECG	X		X	
Echocardiogram	X		X	
Cardiac MRI (adults)	X		X ²	
T2 MRI brain (adults)	X			X
Ophthalmology	X			X
Audiology	X			X
Laboratory Investigations				
Full blood count	X		X	
Urea & electrolytes & creatinine	X	(X)	X	
Spot urine albumin/creatinine ratio or protein/creatinine ratio.	X	(X)	X	
Other tests as indicated				
Lipid profile	X	(X)	X	
Plasma Lyso-Gb3	X	(X)	X	
Highly-sensitive Troponin	X	(X)	X	

9.0 Stopping Criteria

Fabry specific therapy may be withdrawn under the following circumstances:

9.1 General:

- Intolerable and unavoidable adverse effects.
- Intercurrent illness, where either long-term quality of life or expected survival is such that the patient will gain no significant benefit from specific treatment for Fabry disease.
- At the request of the patient, or properly allocated guardian acting in the patient's best interests, if the patient is properly deemed not competent.
- If the circumstances of the patient's lifestyle are such that sufficient compliance with treatment is not possible.
- If the health and wellbeing of medical and / or nursing staff are placed under significant threat as a result of the actions or lifestyle of the patient.
- Emigration of the patient outside the jurisdiction of the UK, when administration and funding of the treatment becomes the responsibility of Health Services in the new country of residence / domicile.

9.2 Specific:

Objective evidence of progression in measured clinical criteria which are not

- Attributable to a secondary pathology
- Commensurate with natural age-related decline
- Remediable by changing product or institution of other simple therapeutic measure.
- Within the normal measured variation of that laboratory parameter.
- Out-weighed in clinical significance by stabilisation or improvement in one of the other criteria

On the basis of current major criteria these might include:

- Deterioration of eGFR by more than 4 ml/min/1.73m²/year and / or requiring renal replacement therapy
- Progressive impairment of systolic or diastolic dysfunction resulting in worsening heart failure symptoms
- Gain in LVMI > 6 gm / m² over a three year period
- Rhythm disturbance requiring therapeutic device insertion in the absence of other demonstrable benefit
- New presentation of clinically significant neurovascular disease in the absence of other demonstrable benefit
- Worsening of pain or gastrointestinal symptoms beyond baseline or no improvement if these are the only reasons to start treatment
- Failure of reduction of plasma lysoGb3 or increase after initial response

Note: in patients with a known cardiac variant form, without any other significant organ involvement then cardiac assessment alone is an appropriate tool for decision making.

10.0 Other cost reducing/saving measures

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 an increased BMI the dose will be capped as for a BMI of 27 kg/m².

Vials will be used in integer units with alternating vials if needed to ensure the most cost effective use. No drug will be wasted.

11.0 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 monitoring will proceed according to the oral protocol if appropriate.

For patients ceasing all Fabry-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.

For patients ceasing Fabry-specific therapy due to environmental factors or failure of compliance they should continue to be monitored by the specialist centre at 6 monthly intervals and the factors leading them to stop therapy be re-evaluated to enable Fabry-specific therapy to be recommenced at the first appropriate opportunity.

Appendix 1: Guidelines for Paediatric (< 16 years) Fabry Disease

1.0 First line therapy: Drug Name (Generic/commercial)

Agalsidase alfa / Replagal
Agalsidase beta / Fabrazyme

2.0 ERT: Children < 16 years with a confirmed diagnosis of Fabry disease and meeting treatment initiation criteria

Fabrazyme 1 mg/kg every other week
or
Replagal 0.2 mg/kg every other week

3.0 Oral chaperone therapy:

Migalastat (Galafold) is not currently licensed for use in children.

For patients aged less than 18 years who meet the conditions set out in a NICE TA/HST or NHS England policy relating to adults: refer to: <https://www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf>.

4.0 Patient Group/Diagnosis

All paediatric patients with a confirmed diagnosis of Fabry disease fulfilling treatment criteria. Diagnostic criteria as documented for adults with Fabry Disease.

5.0 Starting Criteria (one or more of the following):

Children < 16 years:

Disease-modifying therapies should be considered when there are documented Fabry related clinical manifestations. There is no evidence currently that treating asymptomatic children prevents disease progression in classical and later onset variants.

5.1 Evidence of Fabry related renal disease (one of):

- Persistent microalbuminuria (3 consecutive early morning urine samples or 3 random early morning urine samples over a period of six months)
- Reduction in estimated / measured GFR (after a review by nephrologist and other causes have been excluded).

5.2 Evidence of Fabry related cardiac disease (one of):

- LV mass index by 2D echo / cMRI above normal for age or increased by 2SD over a 12 to 24 month period
- ECG: arrhythmias, shortening or prolonged PR interval on age appropriate ECG analyses

5.3. Evidence of general symptoms of Fabry disease:

5.3.1 Isolated neuropathic pain:

- Acroparesthesia confirmed by the LSD physician to be Fabry specific should be sufficient to consider ERT.

Comments:

Whilst analgesia for acroparesthesia must be considered for a minimum period of 6 months in a child less than ten years of age, neuropathic pain is frequently the first Fabry symptom in children and hence defines a more severe cohort. This occurs in approximately 60% of children with “classic” *GLA* gene variants.

5.3.2 Unexplained gastrointestinal (GI) symptoms affecting quality of life

Comments:

Common causes for childhood GI symptoms such as food allergies, coeliac disease, or infections must be excluded first; prior to considering ERT for GI symptoms in children. Review by a gastroenterologist to ensure all common causes for GI symptoms are excluded with / without GI endoscopy is recommended.

6.0 Exclusion for starting disease modifying treatment

The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by enzyme replacement therapy.

7.0 Efficacy measures (with goals):

Children < 16 years:

- Age appropriate paediatric pain tools / devices (improvement)(examples could include VAS, BPI, NRS-11, FPHPQ)
- School attendance (improvement)
- Pain medications (reduction)
- Age appropriate quality of life score (improvement)(examples could include EQ-ED or FPHPQ)
- Growth and development (improvement / or stabilisation if normal)

Comments:

Growth and development are infrequently affected in Fabry children. If there are concerns with growth, other causes for faltering growth should be explored without delay.

Chronic kidney disease / end stage renal failure is very rare in children with Fabry disease. A paediatric nephrologist should evaluate children with these manifestations and exclude other causes.

8. Routine Clinical Monitoring in Children < 16 years:

8.1. Boys and girls < 5 years:

Arrange clinical review if indicated.

8.2. Children \geq 5 years and < 10 years:

8.2.1 Boys with classic pathogenic variants:

Frequency of review as clinically indicated by the treating clinician eg. 12 to 24 monthly.

8.2.2. Girls and boys with late-onset variants:

Frequency of review as clinically indicated by the treating clinician eg. 24 to 36 monthly.

- Clinical review
- School attendance
- Growth and development
- Pain and QoL questionnaires
- Urine albumin/creatinine ratio (spot urine; 3 x consecutive urine samples if random early morning spot urine abnormal)
- Urine protein/creatinine ratio (random spot urine)
- Plasma lyso-Gb3
- ECG; cardiac ECHO (baseline and thereafter as indicated)
- Ophthalmology with slit lamp examination (baseline and thereafter once every 2 to 3 years as indicated)
- Age specific audiology (baseline and thereafter as indicated)

8.2.3 Boys and girls \geq 10 and < 14 years:

Monitor as above (every 12 months) and include:

- Calculated GFR (Counahan-Barratt [CB] method or Schwartz)
- MRI brain if clinically indicated only (stroke/symptoms of TIA/other neurological symptoms. Arrange review by a paediatric neurologist and other causes excluded)

8.2.4 Boys and girls \geq 14 and <16 years:

Monitor as above (every 12 months) and include:

- Cardiac MRI (optional but preferred)
- Measured GFR once every 3 years, with calculated GFR (CB method) annually
- Baseline MRI brain (if clinically indicated)
- Audiology at 14 years and thereafter as clinically indicated

9.0 Stopping Criteria in children

- Severe life threatening infusion associated reactions that cannot be managed by standard protocols, including desensitisation
- Other life threatening / life limiting illness
- Poor compliance – consider a safe-guarding referral if deemed appropriate
- End stage renal failure due to other causes that cannot be treated, or that is not suitable for renal transplant when there are no other Fabry specific symptoms.

Appendix 2

Annual Guideline Audit Form

Date	
Specialist Centre	
Completing Physician	
Total Number NHSE Fabry patients	
New NHSE Fabry patients in review period	
Number of new NHSE Fabry patients commencing ERT / PCT	
Number of new NHSE Fabry patients managed without ERT / PCT	
Number of new patients stopping ERT	
Proportion of patients receiving a nonstandard dose of ERT (%)	
Proportion of patients with clinical events as defined below (%)	

Protocol audit (adults):

1. Dose and therapeutic agent for patients commencing therapy
2. Reason for commencing therapy
3. Patients stopping therapy
4. Proportion of patients with non-standard dose
5. Proportion of patients receiving Fabry-specific therapy
6. Proportion of patients with clinical events after receiving therapy for ≥ 3 years
 - New cardiac arrhythmia or device insertion
 - New ESRF or requirement for renal replacement therapy
 - New stroke

Protocol audit (children):

1. Dose and therapeutic agent for children commencing ERT
2. Reason for commencing therapy
3. Clinical events in children after receiving ≥ 5 years of ERT
4. Fabry specific ECG / Cardiac ECHO abnormalities
5. Onset of microalbuminuria / proteinuria
6. Emergence of neuropathic pain whilst on ERT