HSE Prescribing Protocol

Sebelipase alfa (Kanuma®)

for the Treatment of Lysosomal Acid Lipase Deficiency

This document is intended for use by healthcare professionals only.

While the guidance is intended to strengthen clinical management of these patients, it does not replace clinical judgment or specialist consultation.

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Sebelipase alfa Prescribing Protocol

This sebelipase alfa prescribing protocol has been reviewed by a group of prescribing physicians and healthcare professionals working in the treatment centres of excellence in Ireland. The protocol is designed to standardise practice and support the implementation of treatment pathways for patients in Ireland. The protocol will be reviewed at regular intervals and additionally as new evidence emerges. This protocol should be used in conjunction with the full prescribing and administration details in the sebelipase alfa (Kanuma®) Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/kanuma-epar-product-information_en.pdf[1]

Enzyme Replacement Therapy Steering Committee Position Statement:

The enzyme replacement therapy (ERT) outlined in this protocol should be initiated in an appropriate setting for the management of Lysosomal Acid Lipase Deficiency (LALD). Patient care should be managed by specialist, consultant led, LALD experienced multidisciplinary teams who are part of the tertiary treatment centre at The National Centre for Inherited Metabolic Disorders in CHI at Temple Street or at the Mater Misericordiae University Hospital. Applications to assess patient eligibility for HSE reimbursement for treatment with ERT are made to the ERT steering committee through these centres of excellence (see section 4.2).

Paediatricians will undertake to refer patients to the adult centre on reaching the age of 16-18 years. Adult and paediatric centres undertake to ensure as much as possible a seamless transfer of care.

Collaboration between the tertiary treatment centres and local primary and secondary care services is imperative to ensuring LALD patients receive high standards of care. Local primary and secondary care clinicians will undertake to ensure all LALD patients are referred to the specialist team in the tertiary centre for review/ input. They will endeavour to support local colleagues wherever necessary.

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

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Part 1: HSE Prescribing Protocol for Sebelipase alfa for the Diagnosis and Treatment of Lysosomal Acid Lipase Deficiency (LALD) Patients with Early Onset LALD less than 12 months

1.1 Diagnosis of early onset LALD[2]

Biochemical: documented decreased LAL activity relative to the normal range of the laboratory performing the assay. If there is strong clinical suspicion of infantile onset LALD then the laboratory should be contacted by the clinical team to prioritise the sample.

and/or

Genetic: documented result of molecular genetic testing confirming a diagnosis of LAL Deficiency. Confirmation of the deficient enzyme by *LIPA* sequencing is recommended but the diagnosis is usually established by the clinical findings and enzyme levels so initiation of therapy should not wait for DNA confirmation. Finding of the common mutation c.894G>A would suggest a late onset phenotype but other genotype-phenotype correlations have not been made.

1.2 Sebelipase alfa treatment for patients with early onset LALD less than 12 months[1]

The recommended starting dose in infants presenting with rapidly progressive LALD is 1 mg/kg administered as an intravenous infusion once weekly, escalating to 3mg/kg at the discretion of the physician. It may be necessary to start at 3mg/kg in the presence of significant clinical disease. Mortality in the CL03 and CL08 trials appeared to be related to disease severity at onset, with some infants deteriorating rapidly after diagnosis.

Dose escalation to 5mg/kg should be considered based on response to clinical and biochemical criteria, including, e.g., poor growth (especially mid-upper arm circumference, MUAC), deteriorating biochemical markers (e.g. liver transaminases, ferritin, C-reactive Protein, and coagulation parameters), persistent or worsening organomegaly, increased frequency of intercurrent infections, and persistent worsening of other symptoms (e.g. gastrointestinal symptoms).

Further dose adjustments can be made on an individual basis based on achievement and maintenance of therapeutic goals. The clinical trials allowed for reduction of the dosing frequency to alternate weekly, however this was not well tolerated and is not recommended[3]. Clinical studies evaluated doses ranging from 1 to 5 mg/kg once weekly, with one patient receiving a higher dose of 7.5 mg/kg once weekly. Doses higher than 7.5 mg/kg have not been studied.

1.3 Eligibility and starting criteria for sebelipase alfa treatment for patients with early onset LALD less than 12 months[3]

- Patient must attend for medical appointments and investigations as determined by the clinical team.
- Confirmation of decreased LAL activity (usually in leukocytes). A documented molecular genetic test confirming LAL deficiency is helpful.
- Likely phenotype of rapidly progressive LALD with symptoms less than 12 months of age or a history of a sibling with a rapidly progressive course of LALD.

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1.4 Exclusion criteria for sebelipase alfa treatment for patients with early onset LALD less than 12 months[3]

- Clinically important concurrent disease or co-morbidities, which, in the opinion of the specialist team, would not benefit from treatment of the underlying LALD.
- End stage manifestations of LALD that mean the patient would be unlikely to benefit from therapy, including but not limited to multi-organ failure.

1.5 Baseline and follow up monitoring for patients with early onset LALD less than 12 months[2,3]

Once diagnosed, patients should undergo regular comprehensive assessments to evaluate the outcomes of therapy. Table 1: Recommended schedule of assessments for infants presenting less than 12 months

Assessment	Baseline	Weekly for 3 months	Monthly for 1 year	3 monthly	6 monthly
Clinical Examination	X	X	X	X	
Dietetic assessment	X	X	X	X	
Height (length), weight, head circumference, mid upper arm circumference	X	X	X	X	
DNA for *LIPA* mutation analysis (patient)	X				
DNA for *LIPA* mutation analysis (parents)	X				
Full blood count & film, urea & electrolytes, liver profile (including AST, GGT and albumin), lipid profile, ferritin, CRP, LDH	X	X	X	X	
Coagulation profile	X				X
Vitamin A/D/E, essential fatty acids	X				X
Alpha-fetoprotein	X				X
Anti-drug antibodies/ oxysterols	X				X
Immunoglobulins, B/T lymphocyte subsets	X[#]				
Abdominal ultrasound (volumetric for liver and spleen)	X*			X**	
Abdominal MRI (when possible and if appropriate)	Annually*				

[#] may require repeat if abnormal

*If concerns regarding suspicious lesions are raised on imaging, liver biopsy may be indicated

**3 monthly for the first year then 6 to 12 monthly

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1.6 Stopping criteria for sebelipase alfa treatment for patients with early onset LALD less than 12 months[3]

- The patient is diagnosed with an additional progressive life-limiting condition where treatment with sebelipase alfa would not provide long-term benefit.
- The patient develops a life threatening complication unlikely to benefit from further ERT.
- Evidence of disease progression (non-responder - as outlined below) despite regular ERT at an optimised dose and other supportive management strategies (especially nutritional).

Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of relevant clinical information to assess their on-going care needs.

1.7 Measuring sebelipase alfa treatment response for patients with early onset LALD less than 12 months

Patients should receive one year of treatment at a stable dose before an assessment of response is made before considering discontinuation.

Non-responders are defined as having continued disease progression despite regular ERT for at least 1 year fulfilling **3** of the following criteria:

- Persisting faltering growth despite ERT and nutritional interventions (failure to show progressive growth along a centile line for weight and or height and or mid-upper arm circumference).
- No improvement in ALT or other parameters of liver injury, should they have been present at treatment initiation.
- No improvement in LDL-c or other parameters of lipid metabolism disorder, should they have been present at treatment initiation.
- Increased portal vein pressures or *de novo* evidence of portal hypertension on ultrasound and Doppler, or new clinical presentation of portal hypertension (e.g. oesophageal varices)

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Part 2: HSE Prescribing Protocol for Sebelipase alfa for the Diagnosis and Treatment of Late onset Lysosomal Acid Lipase Deficiency (LALD) Patients from 12 months to 18 years

2.1 Diagnosis of late onset LALD[2]

Biochemical: documented decreased LAL activity relative to the normal range of the laboratory performing the assay. If there is strong clinical suspicion of LALD then the laboratory should be contacted by the clinical team to prioritise the sample.

and/or

Genetic: documented result of molecular genetic testing confirming a diagnosis of LAL Deficiency. Confirmation of the deficient enzyme by *LIPA* sequencing is recommended but the diagnosis is usually established by the clinical findings and enzyme levels so initiation of therapy should not wait for DNA confirmation if symptoms are rapidly progressive. Finding of the common mutation c.894G>A would suggest a late onset phenotype but other genotype-phenotype correlations have not been made.

2.2 Sebelipase alfa treatment for patients with late onset LALD from 12 months to 18 years[1]

The recommended dose in children and adults who do not present with rapidly progressive LAL deficiency prior to 12 months of age is 1 mg/kg administered as an intravenous infusion once every other week. Dose escalation to 3 mg/kg once every other week should be considered based on clinical response.

2.3 Eligibility and starting criteria for sebelipase alfa treatment for patients with late onset LALD from 12 months to 18 years[1,3]

- Patient must attend for medical appointments and investigations as determined by the clinical team. Treatment Agreement has been signed by both parties
- Confirmation of documented decreased LAL activity (usually in leukocytes). Ideally a documented result of molecular genetic testing confirming a diagnosis of LAL Deficiency
- Failure to thrive or growth impairment*

AND at least ONE of the following[1]

- Persistently elevated transaminases (ALT > 1.5 x ULN** and/or AST > 1.5 x ULN**) as measured by two assessments a minimum of one month apart
- Dyslipidaemia with LDL-c > 3mmol/L and/or HDL-c < 1mmol/L despite lipid lowering treatments (with i.e. statins etc.)
- Ideally: Evidence of steatosis AND liver fibrosis by either liver biopsy or FibroScan

* Decreased body weight across >2 of the major centiles on a WHO weight-for-age chart or body weight below 5th centile and/or decreased height across >2 of the major centiles on a WHO height-for-age chart

** ULN = Upper Limit of Normal age and gender specific ALT /AST

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2.4 Exclusion criteria for sebelipase alfa treatment for patients with late onset LALD from 12 months to 18 years[3]

- Clinically important concurrent disease or co-morbidities which, in the opinion of the specialist team, would not benefit from treatment of the underlying LALD
- End stage manifestations of LALD that mean the patient would be unlikely to benefit from therapy, including but not limited to multi-organ failure.
- The patient is unwilling or unable to comply with the associated monitoring criteria, including attending all required clinic visits.

2.5 Baseline and follow up monitoring for patients with early onset LALD from 12 months to 18 years[2,3]

Once diagnosed, patients should undergo regular comprehensive assessments to evaluate the outcomes of therapy. Table 2. Recommended schedule of assessments

Assessment	Baseline	3 monthly	6 Monthly	Annually
Clinical assessment	**X**	**X (for the 1st year)**	**X**	
Dietetic assessment	**X**	**X (for the 1st year)**	**X**	
Height (length), weight, head circumference, mid upper arm circumference	**X**	**X (for the 1st year)**	**X**	
DNA for *LIPA* mutation analysis (patient)	**X**			
DNA for *LIPA* mutation analysis (parents)	**X**			
Liver Biopsy (if available)	**X+**			
FibroScan (if available)	**X**			**X**
Full blood count & film, urea & electrolytes, liver profile (including AST, GGT and albumin), lipid profile, ferritin, CRP, LDH	**X**	**X (for the 1st year)**	**X#**	
Coagulation profile	**X**		**X#**	
Vitamin A/D/E, essential fatty acids	**X**		**X**	
Alpha-fetoprotein	**X**		**X**	
Anti-drug antibodies/ oxysterols	**X**		**X**	
Immunoglobulins, B/T lymphocyte subsets	**X$**			
Abdominal ultrasound (volumetric for liver and spleen) (or if available FibroScan)	**X***			**X***
Abdominal MRI or CT (when possible and if appropriate)				**X***

+ In patients starting treatment with sebelipase liver biopsy should be carried out at appropriate intervals if indicated and available.
#More frequently if abnormal
$May need to be repeated if abnormal
*If concerns regarding suspicious lesions are raised on imaging, liver biopsy may be indicated.

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2.6 Stopping Criteria for Sebelipase alfa treatment for patients with early onset LALD from 12 months to 18 years[1,3]

- The patient is diagnosed with an additional progressive life-limiting condition where treatment with sebelipase alfa would not provide long-term benefit.
- The patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved.
- Evidence of disease progression (non-responder - as outlined below) despite regular ERT at an optimised dose and other supportive management strategies (especially nutritional).
- The patient is unable to comply with assessments for continued therapy.

Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of relevant clinical information to assess their on-going care needs.

2.7 Measuring Sebelipase alfa treatment response for patients with early onset LALD from 12 months to 18 years[1,3]

Patients should receive one year of treatment at a stable dose before an assessment of response is made.

Non-responders are defined as having continued disease progression despite regular ERT for at least 1 year fulfilling **3** of the following criteria:

- Persisting faltering growth despite ERT and nutritional interventions (failure to show progressive growth along a centile line for weight and or height and or upper arm circumference)
- No improvement in ALT or other parameters of liver injury, should they have been present at treatment initiation
- No improvement in LDL-c or other parameters of lipid metabolism disorder, should they have been present at treatment initiation
- Increased portal vein pressures or de novo evidence of portal hypertension on ultrasound and Doppler, or new clinical presentation of portal hypertension (e.g. oesophageal varices)
- No improvement in liver involvement as assessed by MRI, FibroScan or liver biopsy

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Part 3: HSE Prescribing Protocol for sebelipase alfa for the Diagnosis and Treatment of Lysosomal Acid Lipase Deficiency (LALD) Adults Patients Diagnosed over 18 years

Adult patients who presented and were diagnosed with LALD before reaching 18 years and who have not started on treatment will be managed according to Part 2: HSE Prescribing Protocol for sebelipase alfa for the Diagnosis and Treatment of Late onset Lysosomal Acid Lipase Deficiency (LALD) with Sebelipase Alfa for Patients from 12 months to 18 years.

3.1 Diagnosis of late onset LALD in Adult Patients[2]

Biochemical: documented decreased LAL activity relative to the normal range of the laboratory performing the assay.

and/or

Genetic: documented result of molecular genetic testing confirming a diagnosis of LAL Deficiency. Confirmation of the deficient enzyme by *LIPA* sequencing is recommended but the diagnosis is usually established by the clinical findings and enzyme levels. Finding of the common mutation c.894G>A would suggest a late onset phenotype but other genotype-phenotype correlations have not been made.

3.2 Sebelipase alfa treatment for patients over 18 years with late onset LALD[1]

The recommended dose in adults who do not present with rapidly progressive LAL deficiency prior to 12 months of age is 1 mg/kg administered as an intravenous infusion once every other week. Dose escalation to 3 mg/kg once every other week should be considered based on clinical response.

3.3 Eligibility and starting criteria for sebelipase alfa treatment for patients over 18 years with late onset LALD[2,3]

- Patient must attend for medical appointments and investigations as determined by the clinical team. Treatment Agreement has been signed by both parties
- Confirmation of documented decreased LAL activity (usually in leukocytes) and ideally a documented result of molecular genetic testing confirming a diagnosis of LAL Deficiency

AND at least ONE of the following[1]

- Persistently elevated transaminases (ALT > 1.5 x ULN** and/or AST > 1.5 x ULN**) as measured by two assessments a minimum of one month apart
- Persistent dyslipidaemia with LDL-c > 3mmol/L and/or HDL-c < 1mmol/L despite lipid lowering treatments (with i.e. statins etc)
- Ideally: Evidence of significant steatosis and liver fibrosis by either liver biopsy, or FibroScan (NICE Appraisal)

** ULN = Upper Limit of Normal age and gender specific ALT /AST

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3.4 Exclusion criteria for sebelipase alfa treatment for patients over 18 years with late onset LALD [3]

- Clinically important concurrent disease or co-morbidities which, in the opinion of the specialist team, would not benefit from treatment of the underlying LALD
- End stage manifestations of LALD that mean the patient would be unlikely to benefit from therapy, including but not limited to multi-organ failure.
- The patient is unwilling or unable to comply with the associated monitoring criteria, including attending all required clinic visits.

3.5 Follow up and monitoring for sebelipase alfa treatment for patients over 18 years with late onset LALD[2,3]

Once diagnosed, patients should undergo regular comprehensive assessments to evaluate the outcomes of therapy. Table 3 Recommended schedule of assessments

Assessment	Baseline	3 monthly	6 Monthly	Annually
Clinical assessment	X	X (for the 1st year)	X	
Dietetic assessment	X	X (for the 1st year)	X	
DNA for *LIPA* mutation analysis (patient)	X			
DNA for *LIPA* mutation analysis (parents)	X			
Liver Biopsy (if available)	X+			
FibroScan (if available)	X			X
Full blood count & film, urea & electrolytes, liver profile (including AST, GGT and albumin), lipid profile, ferritin, CRP, LDH	X	X (for the 1st year)	X#	
Coagulation profile	X		X#	
Vitamin A/D/E, essential fatty acids	X		X	
Alpha-fetoprotein	X		X	
Anti-drug antibodies/ oxysterols	X		X	
Immunoglobulins, B/T lymphocyte subsets	X$			
Abdominal ultrasound (volumetric for liver and spleen) (or if available FibroScan)	X*			X*
Abdominal MRI or CT (when possible and if appropriate)				X*
Cardiovascular (i.e. ECHO, stress test if indicated)	X			X

+ In patients starting treatment with sebelipase liver biopsy should be carried out at appropriate intervals if indicated and available.
#More frequently if abnormal
$May need to be repeated if abnormal
*If concerns regarding suspicious lesions are raised on imaging, liver biopsy may be indicated.

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3.6 Stopping Criteria for sebelipase alfa treatment for patients over 18 years with late onset LALD [1,3]

- The patient is diagnosed with an additional progressive life-limiting condition where treatment with sebelipase alfa would not provide long-term benefit.
- The patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved.
- Evidence of disease progression (non-responder - as outlined below) despite regular ERT at an optimised dose and other supportive management strategies (especially nutritional).
- The patient is unable to comply with assessments for continued therapy.

Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of relevant clinical information to assess their on-going care needs.

3.7 Measuring sebelipase alfa response in patients over 18 years with late onset LALD [1,3]

Patients should receive one year of treatment at a stable dose before an assessment of response is made

Non-responders are defined as having continued disease progression despite regular ERT for at least 1 year fulfilling 3 of the following criteria:

- No improvement in ALT or other parameters of liver injury, should they have been present at treatment initiation.
- No improvement in LDL-c or other parameters of lipid metabolism disorder, should they have been present at treatment initiation.
- Increased portal vein pressures or de novo evidence of portal hypertension on ultrasound and Doppler, or new clinical presentation of portal hypertension (e.g. oesophageal varices).
- No improvement in liver involvement as assessed by MRI, FibroScan or liver biopsy

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Part 4: Additional Information

4.1 Audit:

Clinical audit should be undertaken on a biennial basis. This audit will specifically review the patient cohort to ensure that clinical outcome targets (measure of efficacy) as listed in this document are reviewed and recorded. A recent EMA audit[4] highlighted the need for disease specific registries for outcome evaluation and benefit-risk monitoring of medicinal products. Clinical research, to include outcome analysis and audit, should play a central role in Centres of Expertise. A top–down approach to support research for Centres of Expertise is recommended.

Financial audit should be undertaken by Acute Hospital Drug Management Programme (AHDMP) in relation to reimbursement of treatment reimbursed centrally. This will specifically monitor the claims made and compliance with eligibility criteria.

4.2 Funding of Treatment:

LALD patients within the public health system will be funded for their treatment with sebelipase alfa by the Health Service Executive (HSE). Prior funding agreement will be sought before initiation of treatment for eligible patients. Once approval for funding has been received (co-ordinated via the Acute Hospitals Drugs Management Programme (AHDMP) ahdmp@hse.ie) treatment can be initiated. All new patients and dose increases for existing patients require prior approval via the Enzyme Replacement Therapy (ERT) committee. Funding approval applications can be made and sent to ahdmp@hse.ie.

4.3 Continued Assessment

Patients are required to attend their Metabolic Clinic as clinically indicated. Any additional appointments and clinics must also be attended. It is recognised that some patients for a variety of reasons may not be able to complete all the assessments listed. All possible efforts should be made to complete as many of the assessments as possible.

Appendix 1.0 Membership of the Enzyme Replacement Therapy Steering Committee (December 2023)

- Chair: Ms Catherine Clarke, Assistant National Director, Acute Operations. Mr Gerry Greville, Interim ACFO, Acute Operation Finance.
- Ms Fionnuala King, Chief Pharmacist, AHDMP.
- Ms Rhona O'Neill, Chief II Pharmacist, AHDMP.
- Ms Lisa Kenny, HSE Primary Care Reimbursement Service Representative.

Representation from Paediatric Centre

- Prof. Ellen Crushell, Consultant Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- Dr Joanne Hughes, Consultant Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.

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- Prof. Ahmad Monavari, Consultant Metabolic Paediatrician, Clinical Director, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- Ms Eithne Losty, Lysosomal Storage Disorders Clinical Nurse Specialist.

Representation from Adult Centre

- Prof. James O'Byrne, Consultant Physician, National Centre for Inherited Metabolic Disorders, Mater Misericordiae University Hospital, Dublin.

Expert advice from

- Dr Emer Fitzpatrick, Consultant Paediatric Hepatologist.

Appendix 2.0 Revision History

Revision number	Revision date	Summary of changes
2.0	January 2024	Part 3 HSE Prescribing Protocol for sebelipase alfa for the Diagnosis and Treatment of Lysosomal Acid Lipase Deficiency (LALD) Adults Patients Diagnosed over 18 years added

References:

1. Summary of Product Characteristics KANUMA 2 mg/ml concentrate for solution for infusion. Available from: https://www.ema.europa.eu/en/documents/product-information/kanuma-epar-product-information_en.pdf. Accessed online: 10/05/2022
2. Kohli, R. *et al.* Initial assessment and ongoing monitoring of lysosomal acid lipase deficiency in children and adults: Consensus recommendations from an international collaborative working group. Molecular Genetics and Metabolism 2020 Feb;129(2):59-66. doi: 10.1016/j.ymgme.2019.11.004. Epub 2019 Nov 18.
3. Consensus expert clinical opinion HSE Enzyme Replacement Therapy Steering Committee October 2022.
4. Report on Pharmacovigilance tasks. EMA. Available from: https://www.ema.europa.eu/en/documents/report/report-pharmacovigilance-tasks-eu-member-states-and-european-medicines-agency-ema-2019-2022_en.pdf. Accessed online: 02/01/2024

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