GIG CYMRU NHS WALES
Cyd-bwyllgor Comisiynu
Joint Commissioning Committee

# Drug Treatment for Lysosomal Storage Disorders (All Ages)

## Commissioning Policy: CP55

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| **Description** | NHS Wales will routinely commission this specialised service in accordance with the criteria described in this policy |
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## Publication History

| **Document Updates** | | | |
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| 5.0 | September 2024 | Imiglucerase (Cerezyme®) has been added as a treatment for Gaucher Type I and III. | 12/09/2024 |
| 5.0 | September 2024 | Alglucosidase alfa (Myozyme®) has been added as a treatment option for Glycogen Storage Disease II (Pompe Disease) | 12/09/2024 |

GIG CYMRU NHS WALES | Cyd-bwyllgor Comisiynu Joint Commissioning Committee

# Contents

# Policy Statement

NHS Wales Joint Commissioning Committee (NWJCC) will commission drug treatments for lysosomal storage disorders (LSDs) for people of all ages in accordance with the criteria outlined in this document.

In creating this document NWJCC has reviewed this clinical condition and the options for its treatment. It has considered the place of each drug treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

## Welsh Language

NWJCC is committed to treating the English and Welsh languages on the basis of equality, and endeavour to ensure commissioned services meet the requirements of the legislative framework for Welsh Language, including the Welsh Language Act (1993), the Welsh Language (Wales) Measure 2011 and the Welsh Language Standards (No.7) Regulations 2018.

Where a service is provided in a private facility or in a hospital outside of Wales, the provisions of the Welsh language standards do not directly apply but in recognition of its importance to the patient experience, the referring health board should ensure that wherever possible patients have access to their preferred language.

In order to facilitate this, NWJCC is committed to working closely with providers to ensure that in the absence of a Welsh speaker, written information will be offered and people have access to either a translator or 'Language-line' if requested. Where possible, links to local teams should be maintained during the period of care.

## Decarbonisation

NWJCC is committed to taking assertive action to reducing the carbon footprint through mindful commissioning activities. Where possible and taking into account each individual patient's needs, services are provided closer to home, including via digital and virtual access, with a delivery chain for service provision and associated capital that reflects the NWJCC commitment.

## Disclaimer

NWJCC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy.

This policy may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian, or Local Authority.

NWJCC disclaims any responsibility for damages arising out of the use or non-use of this policy.

# 1. Introduction

This document has been developed as a policy for the planning and delivery of drug treatments for lysosomal storage disorders (LSDs) for people of all ages and resident in Wales. This service will only be commissioned by the NHS Wales Joint Commissioning Committee (NWJCC) and applies to residents of all seven Health Boards in Wales.

## 1.1 Plain Language Summary

Lysosomal storage disorders (LSDs) are inherited metabolic diseases characterized by an abnormal build-up of harmful substances in the body which may affect different parts of the body; including the bones, brain, skin, heart, and central nervous system. The disorders occur as a result of a missing or damaged enzyme. There are 70 of these disorders altogether and new disorders continue to be identified[1].

LSDs are progressive and the patient's symptoms can worsen over time. There is currently no cure for any of the LSDs. Medicines used to treat these disorders aim to reduce the build-up of harmful substance in the body, which results in a reduction in the speed at which the disease progresses, and over time leads to better outcomes for the patient[2].

Patients with these disorders, including those receiving drug treatments, need specialist medical care and regular multidisciplinary review.

## 1.2 Treatments

Drug treatments given to manage LSDs are disease modifying and are widely used in the United Kingdom. The main aim of treatment is to reduce the severity of symptoms or delay the disease progression. Care for patients with LSDs is provided by specialist centres with experience of each condition and the medications used to treat them. Haematopoietic stem cell transplantation (HSCT) may be used as a therapeutic option in some LSD conditions. In addition, specialist centres provide supportive care to manage the symptoms and complications associated with the condition.

Patients are assessed according to current criteria for suitability of treatment. The criteria vary from disorder to disorder and are constantly reviewed.

[1] Rajkumar V, Dumpa V. Lysosomal Storage Disease. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563270/
[2] Lysosomal Storage Disorders - Symptoms, Causes, Treatment | NORD (rarediseases.org)

Drugs used to treat some of the LSDs include:

- Enzyme replacement therapy (ERT) - given to people who suffer from chronic conditions resulting from enzyme deficiencies or malfunction.
- Substrate reduction therapy (SRT) - given to reduce the amount of harmful substances that the body has to break down.
- Molecular chaperone therapy - assist enzymes in becoming functional by helping them take the correct shape and stay stable.
- Gene therapy - the introduction of normal genes into the body in place of missing or defective ones in order to correct genetic disorders.

Despite there currently being no cure for any of the LSDs, new drug treatments continue to be developed in this rapidly advancing field.

## 1.3 Epidemiology

Although individual LSDs are considered very rare there are a large number of disorders (nearly 50) and thus the prevalence of the group as a whole is about 20 per 100,000 live births. Individually they are very rare with individual incidences ranging from 1:60,000 to 1:1,000,000[3].

## 1.4 Individual disorders

### 1.4.1 Fabry Disease

Fabry disease is an X-linked disorder which affects the way the body breaks down glycosphingolipids (lipids / fats). It is caused by the absent or marked deficient activity of the lysosomal enzyme alpha-galactosidase A. Early childhood symptoms include neuropathic pain. Without treatment the condition progresses throughout adult life to cause serious cardiac, neurological and renal disease.

Fabry disease is a pan-ethnic disorder with an estimated UK prevalence of 2:100,000 births[4]. There are four licensed medicines in the UK for treating Fabry disease; three ERT therapies, agalsidase alfa (Replagal®)[5], agalsidase beta (Fabrazyme®)[6] and pegunigalsidase alfa (Elfabrio)[7] and a chaperone therapy migalastat (Galafold®)[8].

[3] Lysosomal Storage Disorders - NORD (National Organization for Rare Disorders) (rarediseases.org)
[4] Overview | Migalastat for treating Fabry disease | Guidance | NICE
[5] Replagal 1mg/ml concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[6] https://www.medicines.org.uk/emc/search?q=%22Fabrazyme%22
[7] https://www.medicines.org.uk/emc/product/14960
[8] Galafold 123 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

### 1.4.2 Gaucher Disease Types I, II and III

Gaucher disease (GD) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme Beta glucocerebrosidase. GD is the most common type of LSD.

There are three types of GD all of which occur in children, with symptoms sometimes not presenting until adulthood. The first, type I, is the most common and patients in this group usually present with enlargement of the liver and spleen and haematological problems. There are no signs of brain involvement but without treatment serious skeletal complications can occur. In type II GD, liver and spleen enlargement are apparent by three months of age and affected infants have central nervous system (CNS) damage and usually die before their second birthday. In the third category, called type III, liver and spleen enlargement is variable, respiratory disease is common and signs of brain involvement such as seizures become apparent over time. This type of GD is also associated with a specific eye movement abnormality.

Both Type I and those with visceral symptoms with Type III GD respond favourably to ERT. Type II disease does not respond and ERT cannot prevent the neurological decline and is therefore not indicated in these patients. Two ERT products are currently licensed for use in the UK; imiglucerase (Cerezyme®)[9] licensed for Type I and Type III GD and velaglucerase alfa (VPRIV®)[10] licensed for Type I GD. Individualised therapeutic goals may be necessary in children especially those with type III disease. In addition to ERTs, there are two substrate inhibiting drugs licensed for Type I GD; eliglustat (Cerdelga®)[11] indicated for long-term treatment of adults patients, and miglustat (Zavesca®)[12] indicated for patients deemed unsuitable for treatment with ERT.

### 1.4.3 Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a group of disorders associated with specific enzyme deficiencies. In individuals with MPS disorders, deficiency or malfunction of specific lysosomal enzymes leads to an abnormal accumulation of certain complex carbohydrates (mucopolysaccharides or glycosaminoglycans) in the arteries, skeleton, eyes, joints, ears, skin, and/or teeth. These accumulations may also be found in the respiratory system, liver, spleen, central nervous system, blood and bone marrow. All of the MPS diseases have certain characteristics in common, which include deformities of the bones and joints that interfere with mobility and often cause osteoarthritis, especially of the large, weight-bearing joints. All of the MPS diseases except MPS III disease interfere with growth,

[9] Cerezyme 400 Units Powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[10] VPRIV 400 Units powder for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[11] Miglustat 84mg Hard Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[12] Miglustat 100mg Hard Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

causing short stature. Most are inherited as autosomal recessive traits with the exception of MPS II (Hunter syndrome) which is X-linked[13].

Haematopoietic stem cell transplantation (HSCT) is used as a treatment option for the severe form of MPS I (Hurler syndrome), and in some cases of MPSII and MPS VII. For those that require drug treatments, there are a number of ERT medicines licensed in the UK/Europe to treat MPS, laronidase (Aldurazyme®)[14] is licensed for MPS I, idursulfase (Elaprase®)[15] for MPS II, galsulfase (Naglazyme®)[16] for MPS VI, elosulfase alfa (Vimizim®) for MPS IVa[17] and vestronidase alfa (Mepsevii®) for MPS VII (Sly syndrome)[18].

### 1.4.4 Glycogen Storage disease II (Pompe Disease)

Pompe disease is caused by a deficiency of the lysosomal enzyme acid glucosidase (acid maltase) and is classified into two subtypes. The infantile onset presents within the first months of life and is the most severe form of the disease with a rapidly progressive cardiomyopathy, generalised skeletal muscle weakness and respiratory failure. If untreated, this form is fatal by one to two years of age. Late onset Pompe disease can present any time after birth and is characterised by a progressive muscle weakness (with little or no cardiac involvement) which can lead to severe morbidity, respiratory failure and early mortality.

Affected infants often require long periods of time in paediatric intensive care units and many require long term mechanical ventilation. ERT with alglucosidase alfa (Myozyme®)[19] dramatically alters the natural history of the infantile disease but many patients still require long term follow up. Two more ERTs have recently entered the market. Avalglucosidase alfa (Nexviadyme®)[20], is licensed for use in Pompe disease, and has recently been approved for use in the UK by NICE[21]. Cipaglucosidase alfa (Pombiliti®)[22] is

[13] Lysosomal Storage Disorders - NORD (National Organization for Rare Disorders) (rarediseases.org)
[14] Aldurazyme 100 U/ml concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[15] Elaprase 2 mg/ml concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[16] Naglazyme | European Medicines Agency (europa.eu)
[17] Vimizim, INN-elosulfase alfa (europa.eu)
[18] Mepsevii | European Medicines Agency (europa.eu)
[19] Myozyme 50 mg, powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[20] Nexviadyme 100 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[21] Avalglucosidase alfa for treating Pompe disease (TA821) https://www.nice.org.uk/guidance/ta821
[22] Pombiliti 105 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

the latest ERT to be approved by NICE[23] as an option for treating late-onset Pompe disease in adults used in combination with miglustat (Opfolda®)[24].

Pompe disease is estimated to affect approximately 0.3 in 10,000 people with a reported birth prevalence was 0.8 per 100,000 people for the infantile onset form and 1.75 per 100,000 for the late-onset form according to European Orphanet data[25].

### 1.4.5 Niemann-Pick Disease type C

Niemann-Pick type C (NPC) is a progressive neurodegenerative disorder. It is an autosomal recessive LSD that affects infants, children and adults. It is characterised by a defect in the handling of cholesterol and other fats inside cells. Mutations in the NPC genes cause the accumulation of fats in the liver, brain and spleen. There are two subtypes (NPC1 and NPC2) caused by mutations in either the NPC1 or NPC2 gene. NPC1 is the most prevalent: approximately 95% of cases are caused by genetic mutations in the NPC1 gene. The incidence of NPC is currently estimated at 1 in 100,000 live births[26].

Accumulation of lipids lead to a variety of symptoms, including liver and spleen enlargement, liver dysfunction and neurological abnormalities. Children frequently have lack of muscle coordination, loss of muscle tone, spasticity, increased sensitivity to touch and learning difficulties. Young people and adults have psychiatric illness, dementia and progressive neurological deterioration. Most people also have difficulties with swallowing. The age of onset and severity of symptoms varies substantially from person to person. Patients with neurological onset early in life deteriorate faster and have a shorter life expectancy than those with adult onset. Most people with NPC die between the ages of ten and twenty five.

Treatment options for NPC include substrate reduction therapy and management of symptoms and complications. Miglustat[27] is a substrate reduction therapy with a marketing authorisation for treating progressive neurological deterioration in children and adults with NPC. Supportive care is directed toward the specific symptoms apparent in each individual. This may include palliative care.

### 1.4.6 Wolman Disease

Wolman disease is a rare, genetic condition in which there is a complete loss in lysosomal acid lipase (LAL) enzyme activity. LAL deficiency is sub-classified as Wolman disease in

[23] Cipaglucosidase alfa with miglustat for treating late-onset Pomp disease (TA912) www.nice.org.uk/guidance/TA912
[24] Opfolda 65 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[25] Prevalence of rare diseases by decreasing prevalence or cases.pdf (orpha.net)
[26] Consensus clinical management guidelines for Niemann-Pick disease type C (nih.gov)
[27] Miglustat 100mg Hard Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

babies and cholesteryl ester storage disease in children and adults[28,29]. Wolman disease is the severest type of LAL deficiency, presenting in babies and children under 2 years old as rapidly progressing multisystem disease. The condition can be diagnosed by identifying variants in the lipase A lysosomal acid (LIPA) gene, or deficient LAL enzyme activity, fibroblasts or dried blood spots, or through genetic testing.

The prevalence of LAL deficiency in Wales is unknown based on currently available information. It is estimated that approximately 1 baby with the most rapidly progressive disease is born every 4 years. The estimated incidence rate for Wolman disease is less than 1 in 100,000 births, and for cholesteryl ester storage disease, it is 2.5 in 100,000 births.[30,31] LAL deficiency affects males and females equally.

Wolman disease is characterised by intestinal failure and severe malabsorption, growth failure, hepatosplenomegaly and progressive liver fibrosis and cirrhosis (liver damage and scarring of the liver). It normally causes death in the first 6 months of life, usually because of multiple organ failure. For a smaller group of children diagnosed slightly later (under 2 years), there is usually evidence of growth failure in the first 6 months of life. When symptoms of LAL deficiency occur after 2 years old, this is diagnosed as cholesteryl ester storage disease. This condition tends to have less severe presenting symptoms but can lead to hepatic and cardiovascular problems including hepatomegaly, cirrhosis, liver failure, dyslipidaemia and accelerated atherosclerosis. Sebelipase alfa (KANUMA®) is used as an enzyme replacement[32]. Standard care without sebelipase alfa is palliative[33].

### 1.4.7 Alpha Mannosidosis

Alpha-mannosidosis is a rare genetic disease caused by the deficiency of an enzyme called alpha-mannosidase. It is inherited as an autosomal recessive disorder, which means that both chromosome copies carry mutations in the alpha-mannosidase gene MAN2B1, and both parents may be unaffected carriers. Alpha-mannosidase breaks down oligosaccharides and in the absence of this, oligosaccharides accumulate inside cells, resulting in damage of tissues and organs and leading to cell death. This is characterised by skeletal changes, deterioration of bones and joints, muscle weakness, hearing loss, recurring infections and developmental impairment.

[28] National Organization for Rare Disorders. Wolman disease
National Organization for Rare Disorders. Cholesteryl ester storage disease
[29] National Organization for Rare Disorders. Cholesteryl ester storage disease
[30] Aguisanda F, Thorne N, Zheng W. (2017) Targeting Wolman Disease and Cholesteryl Ester Storage Disease: Disease Pathogenesis and Therapeutic Development. Curr Chem Genom Transl Med 11:1–18.
[31] Online Mendelian Inheritance in Man (OMIM). Lysosomal acid lipase deficiency.
[32] KANUMA 2mg/ml concentrate solution - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[33] Overview | Sebelipase alfa for treating Wolman disease | Guidance | NICE

Alpha-mannosidosis can present at infancy, childhood or early adolescence. The onset and severity of symptoms varies widely across a broad spectrum.
The most severe forms of alpha-mannosidosis manifest during infancy and are typically characterised by enlargement of the liver, severe infections and poor survival rates. More moderate disease is associated with slow progression but the characteristics of alpha-mannosidosis are evident and have a substantial impact on physical and mental wellbeing. These characteristics may be absent in people with mild disease[34].

The exact prevalence of alpha-mannosidosis is not known, but has been estimated to be approximately 1 in 500,000[35]. The MPS Society has identified 30 people with alpha-mannosidosis in the UK, although it is expected that there may be more patients whose disease has not been diagnosed[36].

Treatment options are aimed at managing symptoms, delaying progression and improving quality of life. Allogeneic haematopoietic stem cell transplant (HSCT) from a family member or unrelated donor is a treatment option for some patients when clinically indicated, although there are significant risks associated with allogeneic HSCT[37]. Velmanase alfa (Lamzede®) is a long-term enzyme replacement therapy for people with alpha-mannosidosis[38].

### 1.4.8 Metachromatic Leukodystrophy (MLD) Disease

Treatment for Metochromatic Leukodystrophy (MLD) is covered in a separate NWJCC Policy Position Statement (PPS257).

### 1.4.9 Neuronal ceroid lipofuscinosis type 2

Treatment for Neuronal ceroid lipofuscinosis type 2 is covered in a separate NWJCC Policy Position Statement (PPS262).

## 1.5 Aims and Objectives

This policy aims to define the commissioning position of NWJCC on the use of the medicines listed within this policy, for people with the respective LSD.

The objectives of this policy are to:

- ensure commissioning for the use of the medicines listed for LSDs is evidence based

[34] Beck, M. et al. (2013). Natural history of alpha mannosidosis a longitudinal study. Orphanet Journal of Rare Disease 8:88
[35] Malm, D. (2008). Alpha-mannosidosis. Orphanet Journal of Rare Disease 3:21.
[36] The MPS society. What is Mannosidosis? http://www.mpssociety.org.uk/diseases/related-diseases/mannosidosis/
[37] NICE draft scope. Velamanase for treating alpha-mannosidosis
[38] https://www.medicines.org.uk/emc/product/12836

- ensure equitable access to drug treatments for LSDs
- define criteria for people with LSDs to access drug treatments
- improve outcomes for people with LSDs

## 1.6 What NHS Wales has decided

NWJCC has carefully reviewed the evidence for the drug treatments listed within this policy for each LSD and have concluded that:

- There is sufficient evidence to fund the use of drug treatments for LSDs in accordance with the criteria set out in section 2.1
- There is insufficient evidence to support the routine commissioning of drug treatments for LSDs as listed in section 2.4

## 1.7 Relationship with other documents

This document should be read in conjunction with the following documents:

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

- **National Institute of Health and Care Excellence (NICE) guidance**
  - Individual and up to date drug policies are available on: www.nice.org.uk/guidance/.

- **All Wales Medicine Strategy Group (AWMSG) guidance**
  Individual and up to date drug policies are available at: www.awmsg.nhs.wales/medicines-appraisals-and-guidance/

- **Other relevant documents**
  - NHS Standard Contract for Lysosomal Storage Disorders Service (Children). Service Specification. 2013/2014. B (england.nhs.uk) [accessed 26/04/2022].
  - Transition from children's to adults' services for young people using health or social care services (2016) NICE guideline NG43
  - Welsh Government - The Transition and Handover Guidance (February 2022)
  - Transition from children's to adults' services (2023) NICE Quality standards 140

# 2. Criteria for Commissioning

The NHS Wales Joint Commissioning Committee will approve funding of drug treatments for lysosomal storage disorders (LSDs) for people of all ages, in line with the criteria identified in this policy.

## 2.1 Inclusion Criteria

### 2.1.1 Commissioned drug treatments

NWJCC will only approve funding of drug treatments for lysosomal storage disorders (LSDs) as listed in Table 1.

**Table 1: NWJCC commissioned LSD drug treatments**

| Lysosomal Storage Disorder | Drug Treatment |
|---|---|
| Fabry | **Agalsidase alfa** (Replagal®)<br>**Agalsidase beta** (Fabrazyme®)<br>**Pegunigalsidase alfa** (Elfabrio®)<br>**Migalastat** (Galafold®) |
| Gaucher type I | **Eliglustat** (Cerdelga®)<br>**Velaglucerase alfa** (VPRIV®)<br>**Imiglucerase** (Cerezyme®) |
| Gaucher type III | **Imiglucerase** (Cerezyme®) |
| MPS I<br>(Hurler/Hurler-Scheie syndrome) | **Laronidase** (Aldurazyme®) |
| MPS IVa<br>(Morquio syndrome) | **Elosulfase alfa** (Vimizim®) |
| Glycogen Storage Disease Type II (Pompe) | **Alglucosidase alfa** (Myozyme®)<br>**Avalglucosidase alfa** (Nexviadyme®)<br>**Cipaglucosidase alfa** (Pombiliti®) with **miglustat** (**Opfolda**®) |
| Wolman Disease | **Sebelipase** (KANUMA®) |
| Alpha Mannosidosis | **Velmanase alfa** (Lamzede®) |

### 2.1.2 Criteria for Commencing Treatment

To commence drug treatment for LSDs the following criteria should be met:

- A confirmed genetic or enzymatic diagnosis of the relevant LSD, based upon the full assessment of clinical signs and symptoms and a documented deficiency of the relevant enzyme, and DNA variant analysis undertaken where appropriate.
- The patient is under the care of a specialised centre, and treatment is initiated and supervised by specialist physicians experienced in the diagnosis and treatment of LSDs.
- The relevant gatekeeper at Cardiff and the Vale University Health Board has given approval for treatment to commence. (See annex i)
- The drug has marketing authorisation for the condition being treated and is prescribed and administered in accordance with its marketing authorisation.
- The drug is listed as approved for funding within Table 1.
- Drug treatment is prescribed and administered according to agreed local guidelines at the designated centres.
- A Blueteq form is completed prior to commencing treatment (see section 2.6 Blueteq and reimbursement)
- Drugs are purchased by the provider in according to the commercial arrangement where applicable.
- A homecare service provider is used where available and appropriate.

### 2.1.3 Individual Disorders and Treatment Options

NWJCC approve funding for drug treatments in line with the specific recommendations made by NICE or AWMSG as defined in Table 2.

Prior to commencement of drug treatment people should be counselled that if their condition deteriorates during treatment, then drug treatment will be reviewed to assess whether treatment should be stopped.

**Table 2: Individual Disorders and Treatment Options[39]**

| **Fabry Disease** | |
|---|---|
| **Drug treatment** | **Recommendations** |
| **Agalsidase alfa** (Replagal®) | **AWMSG advice 1107: Agalsidase alfa (Replagal®)**<br><br>• Agalsidase alfa (Replagal®) should be recommended for use within NHS Wales as a long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease. |

[39] All treatment options are to be used within their licensed indication and/or marketing authorisation

| | |
|---|---|
| | • Patients receiving agalsidase alfa (Replagal®) will be entered into the Fabry Outcomes Survey.<br>• Treatment will be administered under the supervision of a physician experienced in the management of Fabry disease or other inherited metabolic diseases.<br>• Treatment will be administered according to agreed guidelines at appropriate designated centres. |
| **Agalsidase beta** (Fabrazyme®) | **AWMSG advice 12: Use of agalsidase beta (Fabrazyme®) within NHS Wales**<br><br>**Agalsidase beta (Fabrazyme®) should be endorsed within NHS Wales for the treatment of Fabry disease in accordance with the licensed indication with the following restrictions:**<br><br>AWMSG recommends:<br>• Patients receiving **agalsidase beta (Fabrazyme®) will be entered into the Fabry registry.**<br>• **Treatment will be administered under the supervision of a physician experiences in the management of Fabry disease or other inherited metabolic disease.**<br>• **Treatment will be administered according to agreed guidelines at appropriate centres.** |
| **Pegunigalsidase alfa** (Elfabrio®) | **NICE TA: Pegunigalsidase alfa for treating Fabry disease**<br><br>• Pegunigalsidase alfa is recommended, within its marketing authorisation, as an option for treating Fabry disease in adults It is recommended only if the company provides it according to the commercial arrangement. |
| **Migalastat** (Galafold®) | **NICE HST4: Migalastat for treating Fabry disease**<br><br>• Migalastat is recommended, within its marketing authorisation, as an option for treating Fabry disease in people over 16 years of age with an amenable mutation, only if:<br>  ○ Migalastat is provided with the discount agreed in the patient access scheme, and<br>  ○ only if enzyme replacement therapy (ERT) would otherwise be offered. |

| | |
|---|---|
| **Migalastat (Galafold®)** | **AWMSG Advice 4268: Migalastat For the long-term treatment of adolescents aged 12 years to 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation**<br><br>• Migalastat hydrochloride (Galafold®) is recommended as an option for restricted use within NHS Wales.<br>• Migalastat hydrochloride (Galafold®) is licensed for the long-term treatment of adolescents aged 12 years to 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.<br>• Migalastat hydrochloride (Galafold®) is restricted for use for the treatment of Fabry disease in adolescents aged 12 years to 16 years with an amenable mutation, only if enzyme replacement therapy (ERT) would otherwise be offered.<br><br>This recommendation applies only in circumstances where the approved Patient Access Scheme (PAS) is utilised or where the list/contract price is equivalent or lower than the PAS price. |
| **Gaucher Disease** | |
| **Drug Treatment** | **Recommendation** |
| **Eliglustat** (Cerdelga®) | **NICE HST5: Eliglustat for treating type 1 Gaucher disease**<br><br>• Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers.<br>• Eliglustat is only recommended when the company provides it with the discount agreed in the patient access scheme. |
| **Velaglucerase alfa** (VPRIV®) | **AWMSG advice no 1214: Velaglucerase alfa (VPRIV®)**<br><br>• **Velaglucerase alfa (VPRIV®) is recommended as an option for use within NHS Wales for long-term enzyme replacement therapy in patients with type 1 Gaucher disease.**<br>• **This recommendation applies only in circumstances where the approved Wales Patient Access Scheme is utilised.** |
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| | |
|---|---|
| **Imiglucerase** (Cerezyme®)[40] | **JCC Prioritisation Panel [P26] 2024-2025**<br><br>**Imiglucerase (Cerezyme®) is recommended for non neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease who exhibit clinically significant non-neurological manifestations of the disease.**<br><br>The non-neurological manifestations of Gaucher disease include one or more of the following conditions:<br>• anaemia after exclusion of other causes, such as iron deficiency<br>• thrombocytopenia<br>• bone disease after exclusion of other causes such as Vitamin D deficiency<br>• hepatomegaly or splenomegaly |
| **Mucopolysacharidoses (MPS)** | |
| **Drug Treatment** | **Recommendation** |
| **Laronidase** (Aldurazyme®) | **AWMSG advice: Laronidase (Aldurazyme®)**<br><br>AWMSG would support the use of laronidase (Aldurazyme®) within NHS Wales subject to the following restrictions:<br>**1.** Use of laronidase will be in accordance with:<br>• the drug's Summary of Product Characteristics (SPC), subject to paragraph 2 below, and<br>• agreed uniform service standards and clinical guidelines.<br>**2.** AWMSG recognises that some current uses of laronidase fall outside the drug's SPC (such as its short term use before and after Bone Marrow Transplantation). Any use which falls outside the SPC will only be supported if part of an approved clinical trial.<br><br>Patients from Wales will be treated at either:<br>• the specialist centre for the treatment of lysosomal storage disorders at the University Hospital of Wales, Cardiff, or<br>• one of the six centres which will be nationally designated and funded by the Department of Health under the auspices of the National Specialised Commissioning |

[40] Evidence Summary Review available from NWJCC on request

| | |
|---|---|
| | Advisory Group to provide a service for patients with lysosomal storage disorders.<br>**3.** Having received appropriate consent, details of patients receiving treatment will be entered into the Registry for MPS1 held by the Society for Mucopolysaccharide Diseases (the MPS Society) |
| **Elosulfase alfa** (Vimizim®) | **NICE HST19: Elosulfase alfa for treating mucopolysaccharidosis type 4A**<br>• Elosulfase alfa is recommended, within its marketing authorisation, as an option for treating mucopolysaccharidosis type 4A (MPS 4A) for people of all ages. It is only recommended if the company provides elosulfase alfa according to the commercial arrangement. |
| **Glycogen Storage Disease II (Pompe Disease)** | |
| **Drug Treatment** | **Recommendation** |
| **Alglucosidase alfa** (Myozyme®) | **AWMSG advice: Use of alglucosidase alfa (Myozyme™) within NHS Wales**<br>**Alglucosidase alfa (Myozyme®) is recommended as an option for use within NHS Wales for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).**<br>**Myozyme® is indicated in adults and paediatric patients of all ages.** |
| **Avalglucosidase alfa** (Nexviadyme®) | **NICE TA821: Avalglucosidase alfa for treating Pompe disease**<br>Avalglucosidase alfa (AVAL) is recommended, within its marketing authorisation, as an option for treating Pompe disease in babies, children, young people and adults, only if the company provides AVAL according to the commercial arrangement. |

| | |
|---|---|
| **Cipaglucosidase alfa** (Pombiliti®) **with miglustat** (Opfolda®) | **NICE TA912: Cipaglucosidase alfa with miglustat for treating late-onset Pompe disease**<br>Cipaglucosidase alfa (CIPA) plus miglustat is recommended, within its anticipated marketing authorisation, as an option for treating late-onset<br>Pompe disease in adults. It is recommended only if the company provides CIPA according to the commercial arrangement. |
| **Wolman Disease** | |
| **Drug Treatment** | **Recommendation** |
| **Sebelipase** (KANUMA®) | **NICE HST30: Sebelipase for treating Wolman Disease**<br>Sebelipase alfa is recommended as an option for long-term enzyme replacement therapy in Wolman disease (rapidly progressive lysosomal acid lipase deficiency [LAL-D]), only if people are 2 years or younger when treatment starts. It is recommended only if the company provides sebelipase alfa according to the commercial arrangement. |
| **Alpha Mannosidosis** | |
| **Drug Treatment** | **Recommendation** |
| **Velmanase alfa** (Lamzede®) | **NICE HST29: Velmanase alfa for treating alpha-mannosidosis**<br>Velmanase alfa is recommended as an option for treating the non-neurological signs and symptoms of mild to moderate alpha-mannosidosis, only if:<br>• treatment is started in people under 18 years (it can be continued in people who turn 18 while on treatment)<br>• the company provides it according to the commercial arrangement. |

## 2.2 Continuation of Treatment

Healthcare professionals are expected to review a patient's health at regular intervals to ensure they are demonstrating an improvement or stabilisation of their health due to the treatment being given. This includes optimisation of medicine doses recognising any changes in weight. The patient will continue to receive treatment if they are demonstrating an improvement or stabilisation of their health.

## 2.3 Stopping Criteria

The prescribing clinician should discontinue drug treatment for LSDs if:

- The patient's condition deteriorates whilst receiving drug treatment following maximum escalation of care.
- The patient will not, or cannot comply with the treatment regime after suitable support has been provided by the prescribing clinician, including homecare service provision where applicable.

If treatment is discontinued, the prescribing team will be responsible for stopping the Blueteq form (see section 2.7 Mechanism for Funding).

## 2.4 Exclusion Criteria

NWJCC do not approve funding of drug treatments for lysosomal storage disorders (LSDs) as listed in Table 3 as they have either not been subject to a Health Technology Appraisal (HTA) by NICE/AWMSG or have been previously reviewed and did not receive a positive recommendation.

**Table 3**: **NWJCC non-commissioned LSD drug treatments**

| Lysosomal Storage Disorder | Drug Treatment |
|---|---|
| Gaucher type I | **Miglustat** (Zavesca® ) |
| MPS II<br>(Hunters syndrome) | **Idursulfase** (Elaprase®) |
| MPS VI<br>(Maroteaux-Lamy syndrome) | **Galsulfase** (Naglazyme®) |
| MPS VII<br>(Sly syndrome) | **Vestronidase alfa** (Mepsevii®) |
| Niemann-Pick type C | **Miglustat** (Zavesca® ) |

NWJCC will continue to fund drug treatments listed in Table 3, for people with a lysosomal storage disorder approved for treatment (via the legacy WHSSC / NWJCC prior approval process) prior to the publication of the 2022 revised policy. Retrospective Blueteq forms will not be required for this group of patients.

## 2.5 Transition arrangements

Transition arrangements should be in line with Transition from children's to adults' services for young people using health or social care services NICE guidance NG43 and the Welsh Government Transition and Handover Guidance.

Transition involves a process of preparation for young people and their families for their transition to adulthood and their transition to adult services. This preparation should start from early adolescence 12-13 year olds. The exact timing of this will ideally be dependent on the wishes of the young person but will need to comply with local resources and arrangements.

The transition process should be a flexible and collaborative process involving the young person and their family as appropriate and the service.

The manner in which this process is managed will vary on an individual case basis with multidisciplinary input often required and patient and family choice taken into account together with individual health board and environmental circumstances factored in.

## 2.6 Acceptance Criteria

The service outlined in this policy is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

## 2.7 Mechanism for Funding

The drug treatments listed within this policy as being commissioned, will only be funded for patients registered via the Blueteq system and where an appropriately constructed MDT has approved its use within highly specialised centres

Where the patient meets the criteria listed within section 2.1.2 and the referral is received by an agreed centre, a Blueteq form should be completed for approval.

If the drug treatment is discontinued, it is the responsibility of the prescribing team to discontinue the Blueteq form.

For further information on accessing and completing the Blueteq form please contact NWJCC using the following e-mail address: NWJCCblueteq@wales.nhs.uk

If a non-contracted provider wishes to treat a patient that meets the criteria listed within this commissioning policy, they should contact NWJCC (e-mail: NWJCCblueteq@wales.nhs.uk). They will be asked to demonstrate they have an appropriate MDT in place.

Funding is approved on the basis that drug treatment is prescribed and administered in accordance with its marketing authorisation. If a commercial arrangement is in place, the Health Boards in Wales should refer to the AWTTC Commercial Medicines Access References Tool (CMART) for further information on the Patient Access Scheme (PAS) price.

## 2.8 Patient Pathway (Annex i)

See Annex i.

## 2.9 Service Providers

**Childrens service**
Department of Inherited Metabolic Disease
Children's Hospital for Wales
Heath Park
Cardiff
CF144XN

**Children's service**
Birmingham Children's hospital
Steelhouse Lane
Birmingham
B4 6NH

**Adult service**
Department of Metabolic Medicine
University Hospital of Wales
Heath Park
Cardiff
CF144XN

**Adult service**
Department of Metabolic Medicine
Wrexham Maelor Hospital
Croesnewydd Rd,
Wrexham
LL13 7TD

Onward referral of patients may be considered by the lead clinicians, for each of these services in Cardiff. Shared care arrangements will be made for patients from North Wales

with the National Commissioning Group (NCG) designated centres, in Manchester and Salford, if clinically required.

The Childrens service at the Department of Inherited Metabolic Disease, Children's Hospital for Wales, is supported by the IMD team at Birmingham Children's Hospital.

## 2.10 Clinical Outcome and Quality Measures

The Commissioned provider should work to written quality standards and provide monitoring information to the lead commissioner.

The centre should enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties and for children, teenagers and young adults.

## 2.11 Responsibilities

Referrers should:

- inform the patient and/or their parent or guardian that this treatment is not routinely funded outside the criteria in this policy, and
- refer via the agreed pathway.

Clinicians considering treatment should:

- discuss all alternative treatments with the patient and/or their parent or guardian;
- advise the patient and/or their parent or guardian of any side effects and risks of the potential treatment
- inform the patient and/or their parent or guardian that treatment is not routinely funded outside of the criteria in the policy, and
- confirm that there is contractual agreement with NWJCC for the treatment.

# 3. Evidence

NWJCC is committed to regularly reviewing and updating all of its commissioning policies based upon the best available evidence of both clinical and cost effectiveness.

- **NICE Guidance**
  www.nice.org.uk/guidance/
- **AWMSG Guidance**
  www.awmsg.nhs.wales/medicines-appraisals-and-guidance/

## 3.1 Date of Review

This document is scheduled for review in October 2027 where we will check if any new evidence is available. If no new evidence or intervention is available the review date will be progressed.

If an update is carried out the policy will remain extant until the revised policy is published.

# 4. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable NHS Wales Joint Commissioning Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

This policy has been subjected to an Equality Impact Assessment.

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

An EQIA was also carried out for each commissioned medicines included in this commissioning policy by NICE/AWMSG during their medicines appraisal process. For further details, please refer to the NICE/AWMSG website.

# 5. Putting Things Right:

## 5.1 Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to NWJCC.

## 5.2 Individual Patient Funding Request (IPFR)

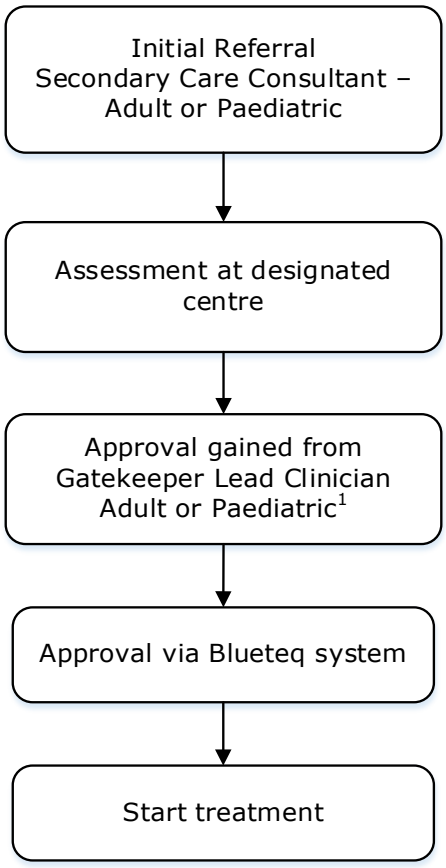
If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Individual Patient Funding Requests

# Annex i Patient Pathway




[1] Onward referral of patients may be considered by the gatekeeper/lead clinicians, for each of these services in Cardiff. Shared care arrangements will be made for patients from North Wales with the NCG designated centres, in Manchester and Salford, if clinically required.

# Annex ii Codes

| Code Category | Disease Area | Code | Description |
|---|---|---|---|
| ICD-10 | Metabolic disorders | E70-E88 | Metabolic disorders |
| | | E76 | Disorders of glycosaminoglycan metabolism |
| | | E75 | Disorders of sphingolipid metabolism and other lipid storage disorders |
| | Pompe Disease | E74.02 | Pompe Disease |
| | | E76.01 | Hurler Syndrome |
| | | E76.02 | Hurler-Scheie Syndrome |
| | | E76.03 | Scheie Syndrome |
| | Mucopolysaccharidosis type II | E76.1 | Hunter Syndrome |
| | Morquio A Mucopolysaccharidoses | E76.210 | Morquio Syndrome |
| | Other mucopolysaccharidoses | E76.29 | Maroteaux- Lamy Syndrome |
| | Other mucopolysaccharidoses | E76.2 | Sly Syndrome |
| | Gaucher Disease | E75.22 | Gaucher Disease |
| | Fabry(-Anderson) Disease | E75.21 | Fabry disease |
| | Niemann-Pick disease type C | E75.242 | Niemann-Pick Type C |
| | Other lipid storage disorders | E75.5 | Wolman Disease |

# Annex iii Abbreviations and Glossary

## Abbreviations

| | |
|---|---|
| **AWMSG** | All Wales Medicines Strategy Group |
| **ERT** | Enzyme replacement therapy |
| **IPFR** | Individual Patient Funding Request |
| **LSD** | Lysosomal storage disorder |
| **NICE** | National Institute for Health and Care Excellence |
| **NWJCC** | NHS Wales Joint Commissioning Committee |
| **SMC** | Scottish Medicines Consortium |
| **SRT** | Substrate reduction therapy |

## Glossary

### Individual Patient Funding Request (IPFR)

An IPFR is a request to NHS Wales Joint Commissioning Committee (NWJCC) to fund an intervention, device or treatment for patients that fall outside the range of services and treatments routinely provided across Wales.

### NHS Wales Joint Commissioning Committee (NWJCC)

NWJCC is a joint committee of the seven local health boards in Wales. The purpose of NWJCC is to ensure that the population of Wales has fair and equitable access to the full range of Tertiary Services. NWJCC ensures that services within our portfolio are commissioned from providers that have the appropriate experience and expertise. They ensure that these providers are able to provide a robust, high quality and sustainable services, which are safe for patients and are cost effective for NHS Wales.