Her family can’t piece together MPS I, but they trust you will

When you see combinations of seemingly unrelated signs and symptoms – including hernia, frequent ear infections, joint contractures, and corneal clouding – consider mucopolysaccharidosis type I (MPS I) and rule it in using a simple urinary glycosaminoglycan (GAG) test.\(^1\,\text{2}\)

---

**SANOFI GENZYME**

Prescribing information can be found at the end of this presentation.

MAT-GB-2103684 (v1.0)

Date of preparation: August 2021

MPS I, Mucopolysaccharidosis type I; GAG, glycosaminoglycan.

Piece together MPS I quickly to help shorten the road to diagnosis for your patients

Patients with MPS I see an average of 5 specialists and wait without answers for approximately 3 years before receiving an accurate diagnosis.¹


MPS I, Mucopolysaccharidosis type I.
MPS I is part of a large group of lysosomal storage disorders (LSDs)\(^1\)

MPS I is 1 of approximately 50 LSDs which cause a pathologic build-up of undegraded storage material in lysosomes.\(^1\)-\(^3\)

Prevalence of any of the ~50 LSD 1: 8,000\(^3\)

---

MPS I, Mucopolysaccharidosis type I; LSD, lysosomal storage disorder.

MPS I is part of a large group of lysosomal storage disorders (LSDs)\(^1\)

MPS I is 1 of approximately 50 LSDs which cause a pathologic build-up of undegraded storage material in lysosomes.\(^1\)\(^-\)\(^3\)

Mucopolysaccharidoses (7 types)

**Prevalence 1:23,000\(^3\)**

**Prevalence of any of the ~50 LSD 1: 8,000\(^3\)**

MPS I, Mucopolysaccharidosis type I; LSD, lysosomal storage disorder.

MPS I is part of a large group of lysosomal storage disorders (LSDs)\(^1\)

MPS I is 1 of approximately 50 LSDs which cause a pathologic build-up of undegraded storage material in lysosomes.\(^1-3\)

**Mucopolysaccharidases (7 types)**

**Prevalence 1:23,000\(^3\)**

**MPS I**

**Prevalence 1:100,000\(^4\)**

Prevalence varies in different populations.\(^5,6\)

---

**MPS I, Mucopolysaccharidosis type I; LSD, lysosomal storage disorder.**

MPS I is a progressive, potentially life-limiting autosomal recessive condition, but the underlying cause can be treated.

The IDUA enzyme – a lysosomal hydrolase – metabolises 2 types of GAGs, dermatan sulphate and heparan sulphate.\(^2\)\(^3\)

Pathogenic variants in the IDUA gene lead to deficient IDUA enzyme activity, which results in lysosomal accumulation of GAGs in many cell types and tissues.\(^1\)

**Consequences of GAG accumulation**

MPS I, Mucopolysaccharidosis type I; GAG, glycosaminoglycan; IDUA, alpha-L-iduronidase.

MPS I presents as a spectrum, with unusual symptom combinations across and within individual phenotypes\textsuperscript{1-3}

The MPS I spectrum:\textsuperscript{1,3-6}

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Severe MPS I: Rapid progression</th>
<th>Attenuated MPS I: Slower progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence in MPS I population</td>
<td>60%</td>
<td>23%</td>
</tr>
<tr>
<td>Median age of onset</td>
<td>6 months</td>
<td>1.5 years</td>
</tr>
<tr>
<td>Early and prevalent signs</td>
<td>Hernia, coarse facial features, kyphosis/gibbus</td>
<td>Hernia, corneal clouding, hepatomegaly</td>
</tr>
<tr>
<td>Median age at diagnosis</td>
<td>1 year</td>
<td>4 years</td>
</tr>
<tr>
<td>Impact on cognition</td>
<td>Significant mental delay with loss of acquired skills</td>
<td>Normal or slightly delayed, learning disabilities</td>
</tr>
<tr>
<td>Life expectancy (if untreated)</td>
<td>&lt; 10 years</td>
<td>Adolescence/early adulthood</td>
</tr>
<tr>
<td>Time between symptom and treatment initiation</td>
<td>&lt; 1 year</td>
<td>2–3 years</td>
</tr>
</tbody>
</table>

MPS I, Mucopolysaccharidosis type I.

Patients with MPS I may live with significant and debilitating disease burden\textsuperscript{1,2}

Multiorgan manifestations and physical deformity can affect both the mental and physical health, quality of life, and life expectancy in patients with MPS I.\textsuperscript{1,2}

As many as 72% of patients with MPS I have a history of early and often seemingly unrelated surgeries.\textsuperscript{3}

Deformity and disability, such as claw hands, coarse facial features, and wheelchair use, may lead to feelings of inadequacy, anger, and depression.\textsuperscript{2}

Hearing loss and speech delays may cause difficulties communicating and lead to poor performance in school.\textsuperscript{2}

For parents, the unique challenges of caring for a child with MPS I may lead to fear, anxiety, frustration, and exhaustion.\textsuperscript{2}

MPS I, Mucopolysaccharidosis type I.

Piecing together MPS I requires a complete physical examination

**Ocular**
- Corneal clouding
- Photophobia

**Auditory**
- Progressive loss of hearing
- Recurrent ear infections

**Respiratory**
- Recurrent ENT infections
- Sleep apnoea

**Cardiac**
- Heart murmurs
- Heart valve thickening

**Neurological**
- Carpal tunnel syndrome (CTS)
- Spinal cord compression

**Gastrointestinal**
- Chronic diarrhoea
- Hepatosplenomegaly
- Hernia

**Musculoskeletal**
- Joint stiffness/contractures
- Poor hand function
- Short stature

---

MPS I, Mucopolysaccharidosis type I; CTS, carpal tunnel syndrome; ENT, ear, nose and throat.

Multiple referrals and surgical procedures in childhood should raise suspicion of MPS I

Other, 8%¹
- Revision/removal of inserted material
- Tooth extraction
- Appendectomy

Eye, 8%¹
- Corneal transplant procedures
- Eye interventions

Neurologic, 5%¹
- Ventriculoperitoneal shunt

Cardiac, 1%¹
- Aortic and mitral valve replacement and reconstruction

Ears, Nose and Throat (ENT), 43%¹
- Myringotomies
- Adenoidectomy
- Tonsillectomy
- Tracheostomy
- Nasal and sinus procedures
- Upper airway interventions

Orthopaedic, 19%¹
- Carpel tunnel release
- Tendon release and trigger finger
- Spinal procedures
- Orthopaedic surgeries

Abdominal/Genitourinary, 21%¹
- Hernia repair
- Genitourinary procedures
- Feeding tubes

Case study #1

Initial presentation

A 6-year-old, developmentally normal girl presented with a 1-year history of stiff and painful joints.

The joints affected included her:

- Hands
- Wrists
- Knees
- Elbows
- Shoulders

Additional medical history at the time of the visit included recurrent otitis media and snoring.

Case study #1

Initial presentation

A 6-year-old, developmentally normal girl presented with a 1-year history of stiff and painful joints.

The joints affected included her:

- Hands
- Wrists
- Knees
- Elbows
- Shoulders

Additional medical history at the time of the visit included recurrent otitis media and snoring.

Based on her presentation she was referred to a rheumatologist.

Rheumatologist assessment

Upon physical examination, multiple joint contractures in the upper extremities were noted.

She received a diagnosis of polyarticular juvenile idiopathic arthritis.

Various treatments were initiated, including:

- Nonsteroidal anti-inflammatory drugs (naproxen)
- Oral and subcutaneous methotrexate
- Intra-articular steroid injections
- Leflunomide

Rheumatologist assessment

Upon physical examination, multiple joint contractures in the upper extremities were noted.

She received a diagnosis of polyarticular juvenile idiopathic arthritis.

Various treatments were initiated, including:

- Nonsteroidal anti-inflammatory drugs (naproxen)
- Oral and subcutaneous methotrexate
- Intra-articular steroid injections
- Leflunomide

All treatments were ineffective.
Second presentation

2 years later at the age of 8, the patient presented with progressive second and third finger numbness.

A nerve conduction study confirmed bilateral carpal tunnel syndrome.
Case study #1

Second presentation¹

2 years later at the age of 8, the patient presented with progressive second and third finger numbness.

A nerve conduction study confirmed bilateral carpal tunnel syndrome.

Following these tests, a lysosomal storage disorder was suspected and she was referred to a metabolic geneticist.

Case study #1

Metabolic geneticist assessment

Upon examination the patient was found to have:

- Flexion contractures
- Multiple joint contractures
- Mild flexion contractures
- Generalised osteopenia


Weight in the 5th percentile  Height in the 3rd percentile  Head circumference in the 10th percentile

Case study #1

Metabolic geneticist assessment

Upon examination the patient was found to have:

- Flexion contractures
- Multiple joint contractures
- Mild flexion contractures
- Generalised osteopenia


Weight in the 5th percentile
Height in the 3rd percentile
Head circumference in the 10th percentile

Based on the history and physical exam findings, GAG analysis and assessment of IDUA enzyme activity were ordered.

GAG, urinary glycosaminoglycan; IDUA, alpha-L-iduronidase.

## Case study #1

### Diagnosis and treatment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme activity was 1 nmol/h/mg and urinary GAG analysis detected excess heparan and dermatan sulphate</td>
<td>Weekly treatment with Iaronidase ERT was initiated</td>
</tr>
<tr>
<td><strong>Attenuated MPS I was confirmed</strong> by genotyping</td>
<td>Improvements in hand mobility and joint size were noted, as well as less joint discomfort</td>
</tr>
</tbody>
</table>

GAG, glycosaminoglycan; ERT, enzyme replacement therapy; MPS I, Mucopolysaccharidosis type I.

Case study #1

Diagnosis and treatment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme activity was 1 nmol/h/mg and urinary GAG analysis detected excess heparan and dermatan sulphate</td>
<td>Weekly treatment with Iaronidase ERT was initiated</td>
</tr>
<tr>
<td><strong>Attenuated MPS I was confirmed</strong> by genotyping</td>
<td>Improvements in hand mobility and joint size were noted, as well as less joint discomfort</td>
</tr>
</tbody>
</table>

MPS I should be considered in the differential diagnosis of paediatric patients with carpal tunnel syndrome and/or joint immobility without an inflammatory component.

GAG, glycosaminoglycan; ERT, enzyme replacement therapy; MPS I, Mucopolysaccharidosis type I.

Case study #2

Orthopaedic surgeon assessment

A male patient first began experiencing **hip pain** at 5 years of age and had **recurrent upper airway tract infections** during childhood till the age 7.

Due to his hip pain, the patient was referred to an **orthopaedic surgeon**.

---

Case study #2

Orthopaedic surgeon assessment

A male patient first began experiencing hip pain at 5 years of age and had recurrent upper airway tract infections during childhood till the age 7.

Due to his hip pain, the patient was referred to an orthopaedic surgeon.

Based on the orthopaedic assessment, the patient was diagnosed with bilateral Legg-Calve-Perthes disease.

Paediatric endocrinologist assessment

At the age of 7, the patient had significant short stature and was referred to an paediatric endocrinologist.

He was treated with:

- Leuprolide acetate (between ages 13-16)
- Recombinant human growth hormone (between ages 14-18)
Case study #2

Paediatric endocrinologist assessment

At the age of 7, the patient had significant **short stature** and was referred to an paediatric endocrinologist.

He was treated with:

- Leuprolide acetate (between ages 13-16)
- Recombinant human growth hormone (between ages 14-18)

**However, the patient was not labelled as growth hormone deficient.**

---

Case study #2

Metabolic disease centre assessment

The patient experienced **sleep apnoea** throughout his teenage years, and was referred to a metabolic disease centre by a respiratory physician who suspected MPS.

Upon examination, the patient was found to have:

- Moderate joint contractures
- Mild facial dysmorphic features
- Scoliosis
- Umbilical hernia
- Short stature (height 154 cm)

Case study #2

Metabolic disease centre assessment¹

The patient experienced sleep apnoea throughout his teenage years, and was referred to a metabolic disease centre by a respiratory physician who suspected MPS.

Upon examination, the patient was found to have:

- Moderate joint contractures
- Mild facial dysmorphic features
- Scoliosis
- Umbilical hernia
- Short stature (height 154 cm)

Based on the history and physical exam findings, assessment of IDUA enzyme activity and genotype analysis were ordered.

IDUA, alpha-L-iduronidase.

## Diagnosis & treatment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDUA activity and genotype analysis confirmed the diagnosis of MPS I</td>
<td>The patient began ERT with laronidase at age 18</td>
</tr>
</tbody>
</table>

---


IDUA, alpha-L-iduronidase; MPS I, Mucopolysaccharidosis type I; ERT, enzyme replacement therapy.
# Case study #2

## Diagnosis & treatment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDUA activity and genotype analysis confirmed the diagnosis of MPS I</td>
<td>The patient began ERT with laronidase at age 18</td>
</tr>
</tbody>
</table>

MPS I should be considered in any patient with short stature and/or growth failure plus one or more of the common signs and symptoms of MPS I.

---

Due to symptom overlap with other diseases, MPS I can often get overlooked leading to delayed diagnosis and treatment, particularly for those with attenuated phenotypes\textsuperscript{1-4}

Symptom overlap with common diseases:\textsuperscript{1,3,5-10}

<table>
<thead>
<tr>
<th>Symptom</th>
<th>MPS I</th>
<th>Juvenile rheumatoid arthritis</th>
<th>Progressive pseudorheumatoid dysplasia</th>
<th>Hypothyroidism</th>
<th>Skeletal dysplasia</th>
<th>Other MPS types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth retardation</td>
<td>×</td>
<td></td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Joint contractures</td>
<td>×</td>
<td>×</td>
<td></td>
<td>×</td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Skeletal manifestations</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>×</td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Hernia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
</tbody>
</table>

Suspect MPS I alongside any of these other diseases with similar progressive symptoms.\textsuperscript{1,3,5-10}

MPS I, Mucopolysaccharidosis type I.

\begin{itemize}
\item[8.] Rastogi \textit{et al.} \textit{Orphanet J Rare Dis}. 2010;5:17.
\end{itemize}
MPS I can be diagnosed with a urinary GAG test, if the test results are abnormally high refer to a metabolic specialist\textsuperscript{1-3}

Click on a specialist centre below for further information:

GAG, glycosaminoglycan.

Early diagnosis and initiation of disease-specific management can change the course of the disease\textsuperscript{1-4}

In a case study of a sibling pair, early diagnosis and treatment limited the progression of attenuated MPS I in the younger sibling:\textsuperscript{1,2}

**Older sister**

Age of diagnosis: 4.5 years  
Age of ERT initiation: 5 years  
Age 16:  
Progression of joint disease, cardiac involvement; corneal clouding remain; height in 10th percentile.

**Younger brother**

Age of diagnosis: <5 months  
Age of ERT initiation: 5 months  
Age 12:  
Mild heart involvement, minimal dysostosis multiplex, mild joint stiffness; height above 97th percentile.


**Early intervention and ongoing management is the best approach to delay the progression of MPS I and potentially reverse some of its signs and symptoms.**\textsuperscript{2-4}

MPS I, Mucopolysaccharidosis type I; ERT, enzyme replacement therapy.

MPS I - suspect, test, refer

**Suspect**
Piece together MPS I in the presence of unusual and unexplained symptom clusters.¹,²

**Test**
If you see signs and symptoms indicative of MPS I, request a urinary GAG analysis.³

**Refer**
If the urinary GAG test result shows abnormally high levels of GAGs, refer to a metabolic specialist.³⁻⁵

MPS I, Mucopolysaccharidosis type I; GAG, glycosaminoglycan.

Sanofi Genzyme MPS disease support offering

Free access to a CPD accredited online learning module

An educational presentation on the key features of MPS disease for you or your team

Disease and clinical information which can be sent electronically

If you would like further information, please contact me directly, or sign up for relevant Sanofi Genzyme updates at www.sanofi.co.uk/hcpconsent.
Prescribing Information: Aldurazyme (larondase) 100 U/ml concentrate for solution for infusion
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: 1ml contains 100U (approximately 0.58mg) of larondase. Each vial of 5ml contains 500U of larondase and 1.29mmol sodium. Indication: Aldurazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPS I; α-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease. Dosage and administration: Aldurazyme treatment should be supervised by a physician experienced in the management of patients with MPS I or other inherited metabolic diseases. Administration of Aldurazyme should be carried out in an appropriate clinical setting where resuscitation equipment to manage medical emergencies would be readily available. The recommended dosage regimen of Aldurazyme is 100U/kg bodyweight administered once every week as an intravenous (IV) infusion. The initial infusion rate of 2U/kg/h may be incrementally increased every 15 minutes, if tolerated, to a maximum of 43U/kg/h. The total volume of the administration should be delivered in approximately 3-4 hours. Paediatric: No dose adjustment necessary. Elderly (≥65 years): No data therefore no dosage can be recommended. Renal and hepatic impairment: No data therefore no dosage can be recommended. Contraindications: Severe hypersensitivity (e.g. anaphylactic reaction) to the active substance or to any of the excipients. Warnings and Precautions: Infusion associated reactions (IARs): Patients treated with Aldurazyme should be closely monitored and all cases of IARs, delayed reactions and possible immunological reactions should be reported. Antibody status should be regularly monitored and reported. Almost all patients are expected to develop IgG antibodies to Aldurazyme, mostly within 3 months of initiation of treatment. Patients who have developed antibodies or symptoms of IARs should be treated with caution. Patients with an acute underlying illness appear to be at greater risk for IARs, thus careful consideration should be given to the patient’s clinical status prior to administration. Initial administration of Aldurazyme or upon re-administration (following interruption of treatment) it is recommended that patients be administered pre-treatment medication (antihistamines and/or antipyretics) approximately 60 minutes prior to the infusion, to minimise the potential occurrence of IARs. If clinically indicated, administration of pre-treatment medication with subsequent infusions of Aldurazyme should be considered. In case of a mild or moderate IAR, treatment with antihistamines and paracetamol/ibuprofen should be considered, and/or a reduction in the infusion rate to half the infusion rate at which the reaction occurred. In case of a single severe IAR, the infusion should be stopped until the symptoms have resolved, and treatment with antihistamines and paracetamol/ibuprofen should be considered. The infusion can be restarted with a reduction of the infusion rate to 1/2-1/4 the rate of the infusion at which the reaction occurred. In case of a recurrent moderate IAR or re-challenge after a single severe IAR, pre-treatment should be considered (antihistamines and paracetamol or ibuprofen and/or corticosteroids) and a reduction of the infusion rate to 1/2-1/4 the rate of the infusion at which the previous reaction occurred. If these reactions occur, immediate discontinuation of Aldurazyme is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment are to be observed. Sodium: This medicinal product contains 30mg sodium per vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2g sodium for an adult and is administered in 0.9% sodium chloride intravenous solution. Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Interactions: No interaction studies have been performed. Aldurazyme is an unlikely candidate for cytochrome P450 mediated interactions. Aldurazyme should not be administered simultaneously with chloroquine or procaine due to a potential risk of interference with the intracellular uptake of Aldurazyme. Pregnancy: There are inadequate data on the use of Aldurazyme in pregnant women, thus the potential risk for humans is unknown. Aldurazyme should not be used in pregnancy unless clearly necessary. Breastfeeding: Aldurazyme may be excreted in milk. It is recommended to stop breast-feeding during Aldurazyme treatment. Fertility: no clinical data. Adverse effects: Immunogenicity: Almost all patients developed IgG antibodies to larondase. Most patients seroconverted within 3 months of initiation of treatment; although seroconversion in patients under 5 years old with a more severe phenotype occurred mostly within 1 month. Very common (>1/10): Headache, flushing, nausea, abdominal pain, rash, arthropathy, arthralgia, back pain, pain in the extremity, pyrexia, infusion site reactions. Common (≥1/100 to <1/10): Anaphylactic reaction, restlessness, paraesthesia, dizziness, tachycardia, hypotension, pallor, peripheral coldness, respiratory distress, dyspnoea, cough, vomiting, diarrhoea, angioneurotic oedema, swelling face, urticaria, pruritis, cold sweat, alopecia, hyperhidrosis, musculoskeletal pain, chills, feeling cold, feeling hot, fatigue, influenza-like illness, body temperature increased, oxygen saturation decreased. Unknown: Cyanosis, hypoxia, tachypnoea, respiratory arrest, bronchospasm, erythema, facial oedema, laryngeal oedema, oedema peripheral and extravasation. Please refer to the SmPC for further information. List Price UK: £444.70 for 1 vial. Legal category: POM. Marketing authorisation holder: Genzyme Europe B.V., Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands. Marketing authorisation number: EU/1/03/253/001-003. Further information available from: Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. uk-medicalinformation@sanofi.com. Date of preparation: November 2020.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to the Sanofi drug safety department on Tel: 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com.