INTRODUCTION TO THE MUCOPOLYSACCHARIDOSES
These are rare but serious genetic metabolic disorders

- There are more than 50 distinct LSDs\(^1\).
- They occur in approximately 1 in 5,000–7,000 live births\(^1,2,3\).
- They are caused by a defect in lysosomal function\(^4\).
  - In most LSDs, undegraded waste cannot be removed from cells.

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In most LSDs, undegraded waste cannot be removed from cells.

- Cells continually need to digest foreign materials (e.g. bacteria) and damaged or old cellular components.

**Lysosomes** are cell organelles that contain specific enzymes for digestion and degradation of complex waste molecules.¹

Lysosomes contain complex material

Complex material is broken down by lysosomal enzymes

Degraded waste material is excreted or can be reused

LSD, lysosomal storage disease

MPS is a deficiency in one of the enzymes that degrade glycosaminoglycans (GAGs)

- GAGs (formally known as mucopolysaccharides) are polysaccharide chains and are some of the complex carbohydrates that are normally degraded by lysosomes\(^1\).

**GAGs are\(^2\):**

- Widely distributed throughout the body
- A major component of connective tissue
- A basic substance of skin, cartilage, and bone
- A component of lubricating fluid in joints
- A component of proteoglycans
- Responsible for the regulation of multiple cell processes

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In MPS disorders GAGs accumulate in lysosomes

Cells without accumulation in lysosomes

In mucopolysaccharidoses, there is a complete lack or insufficient activity of an enzyme needed for GAG degradation^1,2^.

Lysosomes become full of undegraded or partially degraded GAG residues^1^–^4^.

Cells with GAG accumulation in lysosomes

Lysosomes increase in both size and number, engorging the cell ultimately limiting normal cell function^1,5^-^10^.

GAG = Glycosaminoglycan.

6. Hendriksz et al. Molecular Genetics and Metabolism: 2013(110);54-64.
MPS disorders are genetically inherited

- MPS occurs in ~1 in 25,000 births with the prevalence varying by region and ethnic background.\(^1\)\(^-\)\(^3\).

**Autosomal inheritance**
(6 out of 7 MPS types)\(^4\),\(^a\)

If both parents are carriers of the dysfunctional allele (r), there is a **1 in 4** chance that a child will have MPS and a **1 in 2** chance that a child will be a carrier.

**X-linked inheritance**
(MPS II)\(^4\)

If the mother is a carrier of the dysfunctional allele (x), there is a **1 in 2** chance that a son will have MPS and that a daughter will be a carrier.

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\(^a\)MPS; Mucopolysaccharidoses; R, normal allele; r, disease allele; X, normal allele; x, disease allele.

11 known enzyme deficiencies cause 7 main MPS types

<table>
<thead>
<tr>
<th>MPS type</th>
<th>Common name</th>
<th>Enzyme deficiency</th>
</tr>
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<tbody>
<tr>
<td>MPS I</td>
<td>Hurler, Hurler–Scheie, Scheie</td>
<td>α-L-iduronidase</td>
</tr>
<tr>
<td>MPS II</td>
<td>Hunter</td>
<td>Iduronate 2-sulfatase</td>
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<tr>
<td>MPS III</td>
<td>Sanfilippo A, Sanfilippo B, Sanfilippo C, Sanfilippo D</td>
<td>Heparan N-sulfatase, (^{\alpha}-\text{N-acetylgalactosaminidase}), Acetyl CoA: (^{\alpha})-glucosaminide acetyltransferase, (^{N})-acetylglucosamine-6-sulfatase</td>
</tr>
<tr>
<td>MPS IV</td>
<td>Morquio A, Morquio B</td>
<td>(^{N})-acetylgalactosamine-6-sulfatase, (^{\beta})-Galactosidase</td>
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<tr>
<td>MPS VI</td>
<td>Maroteaux–Lamy</td>
<td>(^{N})-acetylgalactosamine-4-sulfatase (arylsulfatase B)</td>
</tr>
<tr>
<td>MPS VII</td>
<td>Sly</td>
<td>(^{\beta})-Glucuronidase</td>
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<tr>
<td>MPS IX</td>
<td>Hyaluronidase deficiency</td>
<td>Hyaluronidase 1</td>
</tr>
</tbody>
</table>
MPS are multisystemic disorders\textsuperscript{1}

<table>
<thead>
<tr>
<th>Signs/ symptoms</th>
<th>Skeletal/ muscular</th>
<th>Developmental</th>
<th>Organ system involvement</th>
<th>Ophthalmological</th>
<th>Neurological</th>
<th>Otorhinolaryngological</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal malformations, joint problems, gait disturbance, growth delay/short stature, knee/hip deformities, gibbus deformity</td>
<td>Dysmorphic/coarse facial features, psychomotor retardation, hypotonia</td>
<td>Heart abnormalities, breathing abnormalities, sleep apnea/ sleep disordered breathing, liver and/or spleen enlargement, hearing deficits, recurrent hernia</td>
<td>Clouding of the cornea, retinal degradation, glaucoma/ increased intraocular pressure</td>
<td>Developmental delays, cognitive delays, hyperactivity, autism spectrum disorder, attention deficits, carpal tunnel syndrome</td>
<td>Frequent ear, sinus and tonsil infections, frequent placement of ear tubes, hearing impairment</td>
<td>Skin and hair abnormalities, hydrops fetalis, poor dentition, dental abnormalities, frequent colds/ upper respiratory infections, macroglossia, family history of MPS</td>
<td></td>
</tr>
</tbody>
</table>

1. Clarke et al. JIEMS 2018 (7):1-12
Examples of MPS I, II, III, IVA and VI patients

MPS I
MPS II
MPS IIIA
MPS IIIB
MPS IIIC

MPS IVA
MPS VI

MPS; Mucopolysaccharidoses.
MPS phenotypic variability

- The type of gene mutation and the amount of enzyme activity are primarily responsible for the severity of disease and rate of disease progression\(^1,2\).
- This variation manifests in a wide range of phenotypes presenting major challenges for identification and diagnosis\(^3,4\).
- Disease phenotype classification falls primarily into two categories:
  - **Rapidly Progressive** or classical typically show physical signs and symptoms before the age of 2 years\(^3\).
  - **Slowly Progressive** or non-classical present later in life, from late childhood to early adulthood, with more subtle signs and symptoms\(^3,4\).

3. Hendriksz C. British J. of Hospital Medicine. 2011;72(2);91-95.
Spectrum of symptom severity and rate of disease progression varies significantly between and within MPS disorders\textsuperscript{1-2}.

- No significant enzyme activity.
- Early onset symptoms.
- Severe debilitation during first decade.
- Early death.

- Residual enzyme activity (based on type of mutation).
- Late onset symptoms.
- Debilitating symptoms occur later in life.
- Survival into adulthood.

Images 1&2 (MPS VI), 3&4 (MPS IVA)

Example of a patient with RAPIDLY PROGRESSIVE disease:

Rapidly advancing disease is apparent at an early age.

At 1 year of age

- Facial coarsening is not yet marked.
- Macrocephaly, skeletal abnormalities, fixed flexion of fingers, enlarged abdomen/hepatomegaly and umbilical hernia are evident.
Example of a patient with SLOWLY PROGRESSIVE disease

Unlike the preceding individual with rapidly progressive MPS VI, this male with slowly progressive disease does not show obvious early clinical features.

At 10 years of age

- Facial coarsening not evident. Mild corneal opacity.
- Mild joint restriction, heart valve (mitral insufficiency) abnormality, bone disease progression, dysplasia more evident at adolescence.
DIAGNOSING MPS
Early signs/symptoms can be missed or patients can be misdiagnosed\(^1\)-\(^2\).

A recent publication has identified common and corroborating red flag signs/symptoms to help physicians identify high risk patients\(^3\).

Identifying these signs/symptoms early is important because of the multisystemic nature of MPS and the prevalence of comorbidities, severe disability and early mortality\(^4\).

Additionally, disease-specific treatments are available which have been shown to slow disease progression\(^5\)-\(^6\).

2. Lampe C et al. Rheumatology 2012;51:401-402
3. Clarke et al. JIEMS 2018 (7):1-12
<table>
<thead>
<tr>
<th>Specialty</th>
<th>Signs/Symptoms</th>
</tr>
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<tbody>
<tr>
<td><strong>PAEDIATRICIANS</strong></td>
<td>Short stature/ decreasing growth velocity</td>
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<td>Gibbus</td>
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<td></td>
<td>Developmental delay</td>
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<td></td>
<td>Recurrent ENT-related symptoms or infections</td>
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<td>Enlarged liver and/or spleen</td>
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<td></td>
<td>Inguinal or umbilical hernia, especially recurrent/ history of hernia repair</td>
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<tr>
<td><strong>ORTHOPAEDICS</strong></td>
<td>Bilateral hip dysplasia. Osteonecrosis (Perthes-like)</td>
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<td></td>
<td>Vertebral body abnormality (hypoplasia, beaking, platyspondyly, kyphosis/gibbus)</td>
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<tr>
<td><strong>OTOLARYNGELOGY</strong></td>
<td>Recurrent ear, nose or throat infections</td>
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<td></td>
<td>Upper airway obstruction</td>
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<td></td>
<td>Progressive hearing loss</td>
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<tr>
<td><strong>RHEUMATOLOGY</strong></td>
<td>Unexplained arthropathy (with or without pain)</td>
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<tr>
<td><strong>PAEDIATRIC NEUROLOGY</strong></td>
<td>Developmental delay/ regression</td>
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<tr>
<td></td>
<td>Language delay</td>
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<td></td>
<td>Hyperactivity</td>
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<tr>
<td><strong>CARDIOLOGY</strong></td>
<td>Cardiac valve thickening</td>
</tr>
<tr>
<td><strong>GENERAL PRACTITIONERS</strong></td>
<td>Unexplained arthropathy with or without pain</td>
</tr>
<tr>
<td></td>
<td>Early onset spinal disease</td>
</tr>
<tr>
<td></td>
<td>Joint restrictions/ stiffness or laxity/ hypermobility</td>
</tr>
<tr>
<td></td>
<td>Cardiac valvular disease</td>
</tr>
<tr>
<td></td>
<td>Early corneal clouding</td>
</tr>
</tbody>
</table>

1. Clarke et al. JIEMS 2018 (7):1-12
Corroborating signs/symptoms

- Abnormal skeletal features (such as gibbus, pectus, broad ribs, hypoplastic odontoid, enlarged sella turcica, genu valgus)
- Atypical Mongolian spots
- Carpal tunnel syndrome (bilateral)
- Chronic rhinorrhea
- Clawed hands
- Coarse facial features
- Corneal clouding
- Dental abnormalities
- Developmental delay
- Difficulty opening mouth
- Dilated Virchow-Robin spaces
- Enlarged tonsils/adenoids
- Glaucoma (bilateral)
- Hearing loss
- Heart valve disease
- Hernias, including previous hernia repair
- Hirsutism
- History of hernia repair
- Hydrocephalus
- Joint abnormalities (restricted/ stiffness or hyper-mobility/laxity)
- Kyphosis
- Left ventricular hypertrophy
- Liver and/or spleen enlargement
- Macroglossia
- Multi-systemic involvement
- Nerve compression syndrome
- Psychomotor delay/regression
- Recurrent ear nose and throat infections
- Seizures
- Short stature
- Sleep apnea
- Spinal deformity
- Unexplained arthropathy, with/without pain

Clinical suspicion should lead to urgent referral

**SUSPECT**
Apart from musculoskeletal abnormalities, other common features that are characteristic for most, but not all MPS types, include:

- Short stature
- Developmental delay
- Recurrent ENT infections
- Upper airway obstructions
- Coarse facial features
- Joint restrictions/ laxity
- Corneal clouding
- Noisy breathing and snoring
- Cardiac murmur
- Umbilical/ inguinal hernia
- Enlarged liver and/or spleen

**REFER** based on signs/symptoms and positive biochemical test results.

**DIAGNOSE**
CONFIRMATORY DIAGNOSTIC STEPS
Experienced metabolic specialist and/or clinical geneticist.

1. Clarke et al. JIEMS 2018 (7):1-12
Where there is clinical suspicion, patients should be referred for the following tests:

- **STEP 1:** Urinary metabolic screen, citing suspected MPS
  - Measures total GAGs
  - With positive result or clinical suspicion, further testing for individual GAGs

- **STEP 2:** Enzymology test (*confirmatory step*)
  - Considered the gold standard test

- **STEP 3:** Gene mutation test (*confirmatory step*)
  - Mutation on both alleles (disease may present only on 1 allele)

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International guidelines for the management and treatment of MPS
Recommended MPS management starts with diagnosis and continues with care throughout the patient’s lifetime

**Diagnosis**
- Perform a urinary screening test for GAG substrates to confirm clinical suspicion \(^1\)
- Confirm diagnosis with enzyme activity test in leukocytes or fibroblasts \(^1\)

**Assessments and interventions**
- Ensure comprehensive care by coordinating a multidisciplinary team led by a clinical geneticist or metabolic specialist \(^1\)
- Consider available treatment options and perform ongoing guideline-recommended assessments as part of the patient’s long-term management plan \(^1\)–\(^7\)

**Transition to adult care**
- Establish a formal, site-specific transition strategy to ensure adult providers are knowledgeable in managing these patients and that patients are not lost to follow-up \(^1\)

ERT, Enzyme Replacement Therapy; MPS; Mucopolysaccharidoses.

MPS requires a multidisciplinary approach

Representation of a coordinated care approach consisting of a team of specialists anchored by an experienced metabolic physician/clinical geneticist

- MPS patients should be referred for frequent mandatory examinations to determine the degree of disease progression.

- Appropriate treatment and symptomatic management options include:
  1. adaptive or supportive devices,
  2. physiotherapy,
  3. occupational therapy,
  4. symptom-based medications and,
  5. surgical intervention (particularly high risk spinal surgery).

- Point 5 should be carefully considered and discussed with the patient and care givers, and initiated at the appropriate time.

Summary

- Mucopolysaccharidoses are multisystemic disorders affecting both children and adults.

- Patients present with a broad spectrum of clinical signs/symptoms sometimes resulting in delay in diagnosis or misdiagnosis.

- With strong clinical suspicion, patients should undergo a series of diagnostic tests to confirm or rule out MPS.

- Disease-specific treatments are available which have been shown to slow disease progression.

- A multidisciplinary approach involving healthcare specialists and care assistance is required to achieve long term optimal health outcomes including surgical intervention, ongoing medical support and rehabilitation.
• Indications: Treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).
• Contraindications: Severe or life-threatening hypersensitivity to active substance or any excipients, if hypersensitivity not controllable.
• Precautions: Anaphylaxis and severe allergic reactions; hypersensitivity; infusion reactions; spinal or cervical cord compression; acute respiratory complications; sleep apnoea; sodium restricted diet; pregnancy (category B3); lactation. Efficacy has not been established for patients under 5 years; safety and efficacy have not been established in patients older than 65 years.
• Adverse Effects: Infusion Reactions including anaphylaxis, hypersensitivity, headache, nausea, vomiting, pyrexia, chills and abdominal pain. Most common adverse events include gastroenteritis, otitis media, ear infection, diarrhoea, vomiting, nausea, abdominal pain, pyrexia, chills, infusion site pain, chest discomfort, oropharyngeal pain, dyspnoea, throat irritation, headache, dizziness, paraesthesia, somnolence, neck pain, myalgia, urticaria, flushing, agitation, corneal opacity.
• Dosage and Administration: Treatment should be supervised by an experienced physician or healthcare provider. Recommended dosage is 2 mg/kg body weight given once weekly over approx. 4 hours as IV infusion diluted with 0.9% NaCl injection. Final volume is based on patient’s weight. Pre-treatment with antihistamines with or without antipyretics recommended.


PBS information: This product is not listed on the PBS. Vimizim is available for the treatment of MPS IVA through the Life Saving Drugs Program. Please refer to the LSDP guidelines for details.
Indications: Long-term enzyme replacement therapy in patients with Mucopolysaccharidosis VI (MPS VI, N-acetylgalactosamine 4-sulfatase deficiency, Maroteaux-Lamy syndrome).

Contraindications: None known.

Precautions: Anaphylaxis and severe allergic reactions; immune-mediated reactions; acute cardiorespiratory failure; acute respiratory complications associated with administration; sleep apnoea; infusion reactions; spinal or cervical cord compression; pregnancy (Category B3); lactation. Efficacy and safety have not been established in patients older than 29 years.

Adverse Effects: Infusion reactions, apnoea, pyrexia, respiratory distress, chest pain, dyspnoea, laryngeal oedema, conjunctivitis, abdominal pain, ear pain, arthralgia, pain, rash, chills/rigors, pharyngitis, areflexia, corneal opacity, gastroenteritis, hypertension, malaise, nasal congestion, umbilical hernia, hearing impairment, pruritus, urticaria, headache, nausea, vomiting, angioedema, anaphylaxis, shock, hypotension, bronchospasm, respiratory failure, erythema, pallor, bradycardia, tachycardia, hypoxia, cyanosis, tachypnoea, and paraesthesia.

Dosage and Administration: Treatment should be supervised by an experienced physician. Recommended dosage is 1 mg/kg body weight given once weekly over ≥4 hours as IV infusion diluted with 0.9% NaCl injection to a final volume of 250mL. For patients ≤20 kg or those susceptible to fluid volume overload, consider diluting in 100 mL and decreasing infusion rate. Pre-treatment with antihistamines with or without antipyretics is recommended.


PBS Information: This product is not listed on the PBS. Naglazyme is available for the treatment of MPS VI through the Life Saving Drugs Program. Please refer to the LSDP guidelines for details.
INDICATION: Long-term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I; α-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease.

DOSAGE AND ADMINISTRATION: 100 U/kg (0.58 mg/kg) once weekly as an intravenous infusion. Infusion rate is incrementally increased and based on patient weight - see full PI. Antipyretic and/or antihistamine pre-treatment is recommended 60 min prior to infusion. Dilute prior to use – see full PI. Does not contain preservatives. Treatment should be supervised by a physician experienced in the management of patients with MPS I or other inherited metabolic diseases.

CONTRAINDICATIONS: Hypersensitivity to the active or any of the excipients.

PRECAUTIONS: Anaphylaxis, hypersensitivity, infusion reaction history, acute respiratory disease, compromised respiratory function, acute illness, pregnancy (category B2), lactation, monitor for IgG antibodies. No data in children under 5 years or patients older than 65 years. See full PI.

INTERACTIONS: No interaction data, theoretical interaction with chloroquine or procaine; do not mix with other medicines in the same infusion.

ADVERSE EFFECTS: Anaphylactic and allergic reactions, upper respiratory tract infection, injection site reaction, infusion-associated reactions e.g. flushing, fever, headache, rash, pallor, fatigue, erythema, oedema peripheral, paraesthesia, feeling hot/cold, oxygen saturation decrease, cough, bronchospasm, dyspnoea, urticaria, angioedema, pruritus, chills, vomiting, nausea, arthralgia, diarrhoea, tachycardia, abdominal pain, blood pressure increase - see full PI.

NAME OF SPONSOR: Genzyme Australasia Pty Ltd, 12-24 Talavera Road, Macquarie Park, NSW 2113.
Minimum product information: ELAPRASE® (Idursulfase-rch)
6mg/3ml concentration solution for infusion

- **INDICATION:** Long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).
- **DOSAGE AND ADMINISTRATION:** 0.5 mg/kg of body weight once weekly as an intravenous infusion delivered over 1-3 hours. Infusion rate should not exceed 100 mL/hr - see full PI. Dilute prior to use – see full PI. Does not contain preservatives.
- **CONTRAINDICATIONS:** Hypersensitivity to the active or any of the excipients.
- **PRECAUTIONS:** Hypersensitivity, anaphylactoid/anaphylactic reactions. Late emergent/biphasic anaphylactoid reactions. History of anaphylactoid reactions or of obstructive airway disease. Compromised respiratory function or acute respiratory disease. Patients susceptible to fluid overload. Acute underlying respiratory illness or compromised cardiac and/or respiratory function in patients with fluid restriction. Pregnancy (B2), lactation, children (<16 months), patients > 65 years. See full PI.
- **INTERACTIONS:** No interaction data.
- **ADVERSE EFFECTS:** Hypersensitivity, infusion reactions - anaphylactic/anaphylactoid reactions, rash, pruritis, urticaria, flushing, hypertension, pyrexia, wheezing, hypoxia, dyspnoea, headache, abdominal pain, nausea, dyspepsia, chest pain, infusion site swelling, cyanosis, arrhythmia, tachycardia, hypotension, hypoxia, tachypnea, bronchospasm, swollen tongue, erythema, face/peripheral oedema. See full PI.

**NAME OF SPONSOR:** Genzyme Australasia Pty Ltd, 12-24 Talavera Road, Macquarie Park, NSW 2113.

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