National PBM Drug Monograph
Laronidase (Aldurazyme®)

VA Pharmacy Benefits Management Strategic Health Care Group and the Medical Advisory Panel

Monograph Summary

- **Indications:** Laronidase (Aldurazyme®) is the first enzyme (recombinant α-L-iduronidase) replacement therapy available for the treatment of Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I and for patients with the Scheie form that have moderate to severe symptoms.

- **Efficacy:** Laronidase has been shown to be effective in reducing liver and spleen volume [noninvasive measures of glycosaminoglycans (GAG) storage] and decreasing urinary GAGs excretion. There have also been improvements in respiratory function and cardiac functional capacity, and the effect appears to be maintained with continued therapy. The long-term effects of therapy are hypothesized to improve patient quality of life and life expectancy, however are not established at this time.

- **Safety:** Adverse effects associated with laronidase use were similar when compared to placebo, including infusion related reactions (most common adverse effect requiring intervention). Laronidase treated patients developed antibodies against the enzyme, which did not appear to be associated with specific adverse effects. Most common adverse effects were respiratory tract infections, rash, and injection site reactions. Patients should be pre-medicated with antipyretics and/or antihistamines 60 minutes prior to start of infusion due to potential of infusion related reactions. In the event of a severe hypersensitivity reaction the use of epinephrine should be cautioned due to increased prevalence of coronary artery disease in this population. There are no known contraindications or drug interactions. Long-term safety information on laronidase is not available at this time.

- **Dose:** The recommended dose is 0.58 mg/kg intravenous infusions every week over a 3-4 hour infusion. Patients should be pre-treated with antipyretics and/or antihistamines 60 minutes prior to start of infusion due to potential of infusion related reactions.

- **Comparison with other treatments:** Treatment for patients with MPS I has typically been limited to palliative care and or high-risk therapies for specific complications. Laronidase is the first enzyme replacement therapy for MPS I.

- **Cost:** For a 40 kg patient the cost per year would be $164,890, without taking into consideration administration costs.

- **Recommendations:** Due to the rarity of the disease and limited use in the veteran population, unknown long-term benefits, and high cost of treatment, it is recommended that this agent remain non-formulary at the National and VISN levels. It should be restricted to patients diagnosed with MPS I disorder (MPS I-H, MPS I-HS, and MPS IS with moderate to severe symptoms).

Introduction[1]

Laronidase (Aldurazyme®BioMarin Pharmaceuticals and Genzyme Corporation) received FDA approval for marketing in the US on April 30, 2003. Laronidase is the first recombinant enzyme replacement therapy approved for the treatment of Mucopolysaccharidosis I (MPS I).

Pharmacology[1-6]

Mucopolysaccharidosis (MPS) is a group of inherited autosomal recessive lysosomal storage disorders (LSD). The common feature is intracellular storage and urinary excretion of glycosaminoglycans (GAGs) due to a deficiency in the lysosomal enzyme required for degradation. The accumulation of GAGs leads to disruption of cellular function and physical deformation of various tissues that gradually develop in the first 2 years of life. Patients manifest with multiple organ involvement, organomegaly, dystosis multiples, and facial coarsening.

MPS I (also referred to as Hurler (H), Hurler-Scheie (HS), or Scheie (S) syndrome) is due to a deficiency of the lysosomal enzyme α-L-iduronidase which cleaves the terminal α-L-iduronic acid residues in the GAGs heparan and dermatan sulphate. MPS I has a wide spectrum of clinical severity depending on the subdivision classification. Hurler's syndrome (MPS IH) is the most severe of the three involving progressive development delays, corneal clouding, airway obstruction, cardiac disease, hepatosplenomegaly, severe joint restrictions, and mental retardation. The lifespan of these patients is up to age 10. Patients with Hurler-Scheie syndrome (MPS IHS) have similar medical problems to patients with Hurler's syndrome, however the progression is slower with a lower rate of mental retardation and increased life span into their teens and 20's. Patients with Scheie's syndrome (MPS IS) have less extensive disease and potentially normal lifespan.

The true incidence of MPS is unknown, with estimates of 1 per 22,500, representing 35% of all lysosomal storage disorders, based on a study of LSD diagnosed in Australia.

Treatment for patients with MPS I has typically been limited to palliative care and or high-risk therapies for specific complications including tracheostomy, cardiac valve replacement, and continuous airway pressure. Treatment that can replace the defective enzyme can potentially improve clinical manifestations. Allogenic bone marrow transplantation (BMT) is the only treatment option that has shown improvement in MPS IH prior to laronidase, especially when instituted before 2 years of age. Limitations in the donor pool and high risk of adverse effects limits this therapy option. Laronidase is the first enzyme replacement therapy available for MPS I.

Laronidase is a highly phosphorylated recombinant human α-L-iduronidase made in Chinese hamster ovary cells. α-L-iduronidase enzyme replacement therapy has proven to decrease liver and spleen size and decrease urinary GAG excretion. There have also been improvements in respiratory function and functional walking capacity, and the effect appears to be maintained with continued therapy. The enzyme does not penetrate the central nervous system (CNS), and thus would not be the only treatment option for MPS IH patients, however may be utilized for those awaiting BMT. Long-term safety and quality of life impact of laronidase are unknown.

Pharmacokinetics[1]

The pharmacokinetics of laronidase were evaluated in 12 patients with MPS I who received 0.58mg/kg as a four-hour infusion. After the 1st, 12th, and 26th week infusions:

C_{max}	1.2-1.7 mcg/mL
AUC	4.5-6.9 mcg•hour/mL
Volume of distribution (Vd)	0.24-0.6 L/kg
Clearance	1.7-2.7 ml/min/kg

Elimination half life (t½)	1.5-3.6 hours

FDA Approved Indication(s) and Off-Label Uses [1]

Laronidase is approved for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I and for patients with the Scheie form that have moderate to severe symptoms. Laronidase has been shown to improve pulmonary function and walking capacity. Laronidase has not been evaluated for effects on the central nervous system manifestations of the disorder.

Dosage and Administration[1]

Dosage and infusion rate:

- The recommended dose is 0.58 mg/kg intravenous infusions every week
- The initial infusion rate of 10mcg/kg/hr may be increased every 15 minutes (based on patient tolerance) during the first hour until a maximum rate of 200 mcg/kg/hr is reached. Then the maximum rate should be maintained for the remainder of the infusion. Infusion rate should be slowed if the patient develops infusion related reactions
- Total volume should be delivered over 3-4 hours. Patients with a body weight of 20kg or less should receive a total volume of 100mL. Patients with a body weight of greater than 20kg should receive a volume of 250 mL

For patients weighing 20 kg or less

Total Volume of Aldurazyme infusion = 100mL

2 ml/hr X 15 minutes (10mcg/kg/hr)	Obtain vitals, if stable increase rate to….
4 ml/hr X 15 minutes (20mcg/kg/hr)	Obtain vitals, if stable increase rate to….
8 ml/hr X 15 minutes (50mcg/kg/hr)	Obtain vitals, if stable increase rate to….
16ml/hr X 15 minutes (100mcg/kg/hr)	Obtain vitals, if stable increase rate to….
32ml/hr ~ 3 hours (200mcg/kg/hr)	For the remainder of the infusion

For patients weighing greater than 20 kg

Total Volume of Aldurazyme infusion = 250 mL

5 ml/hr X 15 minutes (10mcg/kg/hr)	Obtain vitals, if stable increase rate to….
10 ml/hr X 15 minutes (20mcg/kg/hr)	Obtain vitals, if stable increase rate to….
20 ml/hr X 15 minutes (50mcg/kg/hr)	Obtain vitals, if stable increase rate to….
40 ml/hr X 15 minutes (100mcg/kg/hr)	Obtain vitals, if stable increase rate to….
80 ml/hr ~ 3 hours (200mcg/kg/hr)	For the remainder of the infusion

- Patients should be pre-treated with antipyretics and/or antihistamines 60 minutes prior to start of infusion due to potential of infusion related reactions (See Precautions)

Instructions for reconstitution and dilution

- Reconstitution and dilution should be performed by aseptic technique
- The product is supplied as a single use 5ml vial with 2.9mg of laronidase. The number of vials necessary is based on the patient's weight. The medication should be stored in the refrigerator (2-8°C, 36-46°F) and allowed to come to room temperature prior to reconstitution
- Laronidase vial should be slightly opalescent and colorless to pale yellow. Do not use if particulate matter and discoloration are observed
- Determination of the total volume should be made based on the patient's body weight
    - 20 kg or less = 100 mL
    - Greater than 20 kg = 250 mL
- The solution must be diluted with 0.1% Albumin (Human) in 0.9% sodium chloride (NaCl) using the chart below. Remove and discard the volume of Albumin (Human) to be added to the 0.9% NaCl infusion bag. Add appropriate volume of Albumin (Human) to the infusion bag and gently rotate

Total Volume of laronidase infusion	Volume of Albumin (Human) 5% to be added	Volume of Albumin (Human) 25% to be added
100 mL	2 mL	0.4 mL
250 mL	5mL	1 mL

- Withdraw and discard a volume of the 0.1% Albumin (Human) in 0.9% NaCl infusion bag equal to the volume of laronidase concentration to be added
- Slowly withdraw the calculated volume of laronidase using caution to avoid excessive agitation. Do not use a filter needle in any step of preparation to avoid agitation since this may denature laronidase and render inactive
- Slowly add proper amount of laronidase to the 0.1% Albumin (Human) in 0.9% NaCl infusion bag using care not to agitate the solution
- Gently rotate the infusion bag to ensure proper distribution. Do not shake solution
- Laronidase should not be mixed with other products in the same infusion
- Diluted solution should be used immediately. It can be refrigerated at 2-8°C if not used immediately. The product expires 36 hours from time of preparation. Do not store diluted solution at room temperature. Discard any unused portion
- Laronidase should be prepared using PVC containers and administered using a PCV infusion set equipped with an in-line, low protein binding 0.2 micron filter

Adverse Effects (Safety Data)[1]

Most common adverse effects were respiratory tract infection, rash, and injection site reaction. The most serious was an anaphylactic reaction consisting of urticaria and airway obstruction, which occurred in one patient. The most common reaction requiring intervention was infusion related reactions.

The data listed below consist of adverse drug reactions occurring in patients treated with 0.58 mg/kg per week of laronidase for 26 weeks in a placebo controlled, double blinded study of 45 patients. All patients were pretreated with antipyretics and antihistamines prior to infusions.

Adverse Effect	Placebo (N=23)	Aldurazyme (N=22)
Respiratory System		
Upper Respiratory Tract Infection	4(17%)	7(32%)
Body as a Whole		
Chest pain	0	2(9%)
Nervous System		
Hyperreflexia	0	3(14%)
Paresthesia	1(4%)	3(14%)
Skin and Appendages		
Rash	5(22%)	8(36%)
Resistance Mechanism		
Abscess	0	2(9%)
Liver and Biliary System		
Bilirubinemia	0	2(9%)
Vascular		
Vein Disorder	1(4%)	3(14%)
Urinary system		
Facial Edema	0	2(9%)
Cardiovascular, General		
Hypotension	0	2(9%)
Dependant Edema	0	2(9%)
Vision		
Corneal opacity	0	2(9%)
Application Site		
Injection Site Pain	0	2(9%)
Injection Site Reaction	2(9%)	4(18%)
Platelet, Bleeding, and Clotting		
Thrombocytopenia	0	2(9%)

Contraindications[1]

There are no known contraindications.

Warnings[1]

Patients may experience infusion related hypersensitivity (see Adverse Effects) reactions. Slowing the rate of infusion and treatment with antipyretic and/or antihistamine can ameliorate mild to moderate symptoms. Caution should be exercised when administering epinephrine with severe hypersensitivity reactions in patients with MPS I due to increased prevalence of coronary artery disease. The risk and benefits of re-administration after a severe hypersensitivity reaction should be weighed, with appropriate resuscitation measures available.

Precautions[1]

Patients should receive antipyretics and/or antihistamines prior to infusion to decrease the possibility of hypersensitivity reactions. If infusion reactions occur: the infusion rate should be decreased, temporarily stopped, and/or additional antipyretics and antihistamines administered.

Pregnancy Category B: There have not been any adequate well-controlled studies in pregnant women. Studies in rats have shown that at a dose 6.2 times the human dose there was no evidence of impaired fertility or harm to the fetus.

Nursing Mothers: It is not known whether the drug is excreted in human milk.
Pediatric Use: It is not known if children younger than 5 respond differently from older children.

Registry: Patients with MPS I should be informed of the registry to better understand the progression of the disease and the requirements for long-term follow-up. Registry is not required, however encouraged. Information is available at wwwMPSIregistry.com and (800) 745-4447.

Look alike sound alike drugs

Pending analyses

Drug Interactions[1]

No formal drug interaction studies performed.

Efficacy Measures[1,6]

Liver and spleen volume – assessed by MRI
Urine GAGs
Joint range of motion
Cardiac function – assessed by ECG and NYHA classifications
Airway obstruction – assessed by PFTs
Eye disease – assessed by visual acuity, examination, and corneal photographs
CNS abnormalities – assessed by brain and cervical cord MRI, and intelligence scales
Height and weight
Enzyme activity – assessed in buccal brushing and leukocyte activity

Clinical Trial[3,6]

Phase I/II open label 52-week study of α-L-iduronidase replacement in 10 patients with Mucopolysaccharidosis I[3]

<table>
<tr><th>Inclusion/ Exclusion</th><th>Dose</th><th>Patient Characteristics</th><th>Results</th></tr>
<tr>
<td>Inclusion
MPS I clinical manifestations and diagnosis confirmation by biological determination of α-L-iduronidase deficiency

At least 5 years of age

Significant physical disease indicative of MPS I: enlarged liver or spleen (1.5x normal) and elevated urinary GAG (>5X normal)

Exclusion
Critically ill

Previous bone marrow transplant

Received an investigational drug or procedure within 30 days of study enrollment

Primary Endpoints:
Reduction in liver and spleen size

Reduction in urinary GAGs

Secondary Endpoints:
Range of motion

Cardiac function

Visual changes</td>
<td>Laronidase 120,000 U/kg IV every week over 3 hours for 52 weeks

3000 U/kg/hr for first hour, then increased up to 61,000 U/kg/hr for 2nd –3rd hours

Length of infusion was increased to 4-6 hours in patients with hypersensitivity reactions

All were pre-medicated with diphenhydramine IV 0.5-1.25 mg/kg 10-30 minutes prior to enzyme infusion</td>
<td>60% male

Age range from 8-22 years

1 MPS IS
1 MPS IH
8 MSP IHS</td>
<td>Mean activity of σ-L-iduronidase activity was 0.04 U/mg prior to infusion and 4.98 U/mg (15% of normal) 7 days after infusion

<table>
<tr><th></th><th>Mean change</th><th>P value</th></tr>
<tr><td>Liver Volume</td><td>↓ 25%</td><td><0.001</td></tr>
<tr><td>Spleen Volume</td><td>↓ 20%</td><td><0.001</td></tr>
<tr><td>Urinary GAGs</td><td>↓63% (53-74%)</td><td><0.001</td></tr>
<tr><td>Height (n=6) (prepubertal pts)</td><td>↑ 6.0cm</td><td>0.001</td></tr>
<tr><td>Weight</td><td>↑3.2 kg (9%)</td><td></td></tr>
<tr><td>Weight rate of growth (n=6) (prepubertal pts)</td><td>↑ 2.17 kg per year</td><td>0.04</td></tr>
<tr><td>Joint restriction -right shoulder</td><td>↓28°</td><td><0.001</td></tr>
<tr><td>Joint restriction -left shoulder</td><td>↓26°</td><td>0.002</td></tr>
<tr><td>Joint restriction -right elbow</td><td>↓7°</td><td>0.03</td></tr>
<tr><td>Joint restriction -left elbow</td><td>↓7°</td><td>0.07</td></tr>
<tr><td>Joint restriction -right knee</td><td>↓3.2°</td><td>0.10</td></tr>
<tr><td>Joint restriction -left knee</td><td>↓3°</td><td>0.09</td></tr>
<tr><td>Apnea and hypopnea (n=7)</td><td>↓61% in episodes per night</td><td></td></tr>
</table>

Reduction in lysosomal storage
o Liver volume decreased by 19-37% in 9 patients, and 5% in 1 patient
o Liver was normal for body weight and age in 8 patients by week 26, and normal for all at week 52
o Mean reduction in urinary glycosaminoglycan excretion reduced by 63% (53-74%, p<0.001), however still above the upper limit of normal

Range of motion
o Greater improvement was seen with greater severity

Cardiac function
o All 10 patients reported an improvement by 1-2 NYHA classes based on serial interviews, no objective data
o Statistically significant difference between functional scores pretreatment vs. 52 weeks (P=0.002)

Ophthalmic changes
o Extent of corneal clouding did not change, several patients reported decreased photophobia and conjunctival irritation

Symptomatic changes
o Patients reported improved endurance and fewer limitations to ADL's, no objective data

Adverse effects</td>
</tr>
</table>

			o 5 patients had transient urticaria of trunk, face, arms, and legs during infusion during week 4 or later, and 4 patients had recurrence at or after week 20 (decrease infusion rate and additional antihistamines given). o 3 patients had urticaria accompanied by angioedema on 9 occasions (with transient hypoxemia on 3 occasions) o The symptoms resolved one hour after the infusion was stopped, and became less frequent and severe as time progressed

Critique
One year study to establish safety and efficacy of laronidase. Study was only able to establish effect on accumulation of GAGs, decrease in liver and spleen size and decrease in urinary GAGs. Open label study, without a control group and with low power to detect a statistical significance. Able to observe trends but unable to determine long-term morbidity and mortality.

Abstracts[6-9]

Abstract[6,7] Beck M, Wraith JE, Clarke L, Kolodny EH, Pastores GM, Muenzer J, A phase 3 study of rhIDHU enzyme therapy for MPS I. J Inherit Metab Dis 2002; 25 Suppl 1:120(abstract).

- Phase 3 multi-centered (5), multi-national (4), randomized, double blinded, placebo controlled study
- 45 total patients received 100 U/kg (n=23) or placebo (n=23) IV once weekly for 26 weeks
- Pretreated 30-60 minutes prior to infusion with antipyretic and antihistamine
- Infusion over four hours, beginning at a rate of 2 U/kg increased every 15 minutes to a maximum of 43 U/kg
- Primary efficacy outcomes: changes in FVC and 6 minute walk test (6MWT), secondary endpoints were somatic components of MPS I
- Mean age of 15.5 years (6-43)
- Mean increase of 5.9% in FVC ($p=0.016$), corresponding to a 11% improvement over baseline
- 38.1 meter improvement in 6 minute walk test ($p=0.066$)
- Hepatomegaly ($p=0.001$) and urinary excretion of GAG ($p<0.001$) were reduced
- Adverse effects reported in both groups were similar. Infusion related reactions was most common adverse event, however the occurrence was reported greater with placebo than laronidase
- It was concluded that laronidase is safe and efficacious in improving FVC, however longer studies are required

Abstract[6.8] Clarke LA, Muenzer J, Kolodny EH, Pastores GM, Beck M, Wraith JE. RHIDU enzyme replacement therapy for MPS I: 24-week extension data. Am J Hum Genet 2002; 71 Supp 1;4:581(abstract).

- 24-week open label extension of the Beck et al. study to evaluate safety and efficacy
- All patients received laronidase treatment, similar to Beck et al. study
- Patients that received laronidase throughout both trials maintained improvement of 5.9% FVC ($p=0.003$) and 42.9 meters in 6MWT ($p=0.005$)
- Patients originally assigned to placebo showed decline of 0.65% FVC and increase of 23.8 meters in 6MWT ($p=0.005$). They also showed reductions in liver volume (12.6%) and urinary GAGs (68.9%)
- Improved joint range of motion and QOL were observed in both groups
- 1 patient (originally assigned to placebo) experienced a severe life threatening infusion reaction related to laronidase therapy
- Other adverse effects were similar

- Significant improvements in respiratory function and walking capacity

Abstract[9] Muenzer J, Clarke LA, Kolodny EH, Pastores GM, Beck M, Wraith JE. Enzyme replacement therapy for MPS I: 36-week interim results of the phase 3 open-label extension study [abstract]. Presented at the American College of Medical Genetics 9th Annual Clinical Genetics Meeting 2003;(abstract).

- 36-week open label extension of the Beck et al. study to evaluate safety and efficacy. 12-week extension of Clark et al. study
- Patients originally assigned to laronidase throughout both trials maintained improvement of 5.4% FVC (p=0.001) and 40.0 meters in 6MWT (p=0.005)
- Patients originally assigned to placebo showed improvement of 2.6% FVC (p=0.065) and increase of 32.4 meters in 6MWT (p=0.023). They also showed reductions in liver volume and urinary GAGs
- In patients with sleep apnea at baseline, patients originally assigned to laronidase maintained decrease of 5.5 events/hr and patients originally assigned to placebo decreased 9.2 events/hr
- Nearly all patients developed anti-rhIDU IgG antibodies, this did not appear to impact safety and efficacy
- Authors concluded that laronidase safely improves respiratory function and functional capacity

Acquisition Cost

Drug	Dose	FSS Price/2.9mg Vial	Drug Cost/40kg Patient/Month	Annual Drug Cost/Patient
Laronidase	0.58 mg/kg weekly	$429.40	$13,741	$164,890

Recommendations

Laronidase has been shown to be effective in the measures of GAG storage: reduction in liver, and spleen volume, and urine GAG excretion. According to abstract data, there have also been improvements in respiratory function and functional capacity, and the effect appears to be maintained with continued therapy. Effects on joint range of motion, vision, skeletal deformities, and height and/or weight rates are yet to be proven. The long-term effects of therapy are hypothesized to improve patient quality of life and life expectancy, however are not established at this time.

Due to the rarity of the disease and limited use in the veteran patient population, unknown long-term benefits, and high cost of treatment it is recommended that this agent remain non-formulary at the national and VISN levels. It should be restricted to patients diagnosed with MPS I disorder (MPS I-H, MPS I-HS, and MPS IS with moderate to severe symptoms).

References

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9. Muenzer J, Clarke LA, Kolodny EH, Pastores GM, Beck M, Wraith JE. Enzyme replacement therapy for MPS I: 36-week interim results of the phase 3 open-label extension study. Presented at the American College of Medical Genetics 9th Annual Clinical Genetics Meeting 2003;(abstract).

Prepared by: Bhairvi Patel, PharmD
Reviewed by: Elaine M. Furmaga, PharmD
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