# Emerging Drug List

## LARONIDASE

<table>
<thead>
<tr>
<th>Generic (Trade Name):</th>
<th>Laronidase (Aldurazyme®)</th>
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<tbody>
<tr>
<td>Manufacturer:</td>
<td>BioMarin Pharmaceutical Inc./Genzyme Corporation</td>
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<td>Indication:</td>
<td>In the United States, this drug is used by patients with Hurler and Hurler-Scheie disorders of mucopolysaccharidosis I (MPS I) and by patients with Scheie syndrome who have moderate to severe symptoms.¹</td>
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<td>Current Regulatory Status:</td>
<td>In Canada, a marketing application has been submitted to obtain an approved indication.² Individual requests to obtain the medication can be made via the Special Access Programme.¹ The US Food and Drug Administration (FDA) has approved Aldurazyme® for use as described in the Indication section above.⁴</td>
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<td>Description:</td>
<td>Human enzyme alpha-L-iduronidase is manufactured using recombinant deoxyribonucleic acid (DNA) technology.¹ The natural alpha-L-iduronidase enzyme is one of several that may be deficient in the lysosomal storage disease MPS I. MPS I typically develops in infancy and childhood. Its ocular, cardiac, arthritic, cognitive, hepatic, splenic and respiratory effects can be mild to severe.³ Depending on the progression and severity of the disease, death may be expected early (in 10 to 20 years) or life expectancy may be unaltered.⁴ The most severe progressive form is called Hurler disease; and the slower progressing variety is Scheie disease. Those who fall in between have Hurler-Scheie disease.</td>
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<td>Current Treatment:</td>
<td>In appropriate patients, a bone marrow transplant (BMT) is an option for those with the Hurler phenotype. This may have a variable response. Most options are palliative or surgical, addressing the complications of the disease as they arise.¹ Newer avenues being explored for lysosomal storage diseases include substrate deprivation and gene therapy.⁷</td>
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<td>Cost:</td>
<td>As this product is not commercialized in Canada, a price was not identified. In the United States, Genzyme has made available a document to serve as a guide for billing and reimbursement with regards to Aldurazyme®.⁸ One American news site quoted the price of a weekly injection of this product to be over US$2,800.⁹</td>
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<td>Evidence:</td>
<td>In a double-blind, multicentre, placebo-controlled study, 45 patients with a documented diagnosis of MPS I were randomized to receive either laronidase 100 units/kg (0.58 mg/kg) or placebo intravenously once weekly for 26 weeks. All patients exhibited reduced alpha-L-iduronidase activity in skin fibroblasts or leukocytes; and 82% of patients were classified as having Hurler-Scheie disease. Exercise tolerance and forced vital capacity (%FVC) were primary endpoints; changes in sleep parameters, liver size and joint mobility were also assessed. After 26 weeks, the drug failed to improve the distance walked during six minutes to a level of statistical significance (mean change 38.1 metres, 95% CI: -2 to 79). Compared with placebo, laronidase produced a signifi-</td>
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A non-randomized extension of this study was ongoing at the time of the original FDA submission. Some data from this extension were included in the clinical review.10

An uncontrolled observational study of 10 patients aged five to 22 years with MPS I who were treated with recombinant enzyme replacement was also described. Patients received open-label laronidase 125,000 units/kg intravenously once weekly for one year. At the end of the study, mean liver and spleen volume decreased on average by 25% and 20% from baseline respectively (P<0.001 for both). Increases from baseline in height and weight were observed in prepubertal patients. The range of motion, as judged by the change in degree of restriction, was likewise increased at the shoulders (p <0.002), elbows (p <0.03) and knees (p <0.10). In those patients with documented apnea on enrolment (n=7), the mean apnea-hypopnea index decreased from 2.1 to 1 event per hour. The New York Heart Association functional classification improved subjectively on patient interview, although objective data to reinforce this finding were lacking. It was not documented that corneal clouding, present in eight patients, improved during therapy.6

A report from this study described immune tolerance after long-term (104 weeks) use of laronidase.11 The authors commented that at enrolment, all patients had low serum antibody titres to the agent, comparable to control serum. During the original trial, half of the patients experienced a rise in antibody titres, although this declined with continued treatment and was lower than baseline by the end of the assessment.11

More data on the experience of four other patients can be found in the FDA submission document.10

Adverse Effects:
The rate of adverse events experienced by laronidase and placebo recipients was similar in the randomized trial. Infusion-related reactions in the clinical trials were generally mild to moderate; one individual died from an immune response to the drug.10 The product’s prescribing information lists upper respiratory tract infection, chest pain, hyperreflexia, paresthesia, rash, abscess, bilirubinemia, vein disorder, facial edema, hypotension, dependent edema, corneal opacity, thrombocytopenia and injection-site reactions or pain being reported in two or more patients when compared with the control group during the 45-person randomized trial. Diminution in infusion rate and premedication with antihistamines were suggested in the clinical trial to minimize or manage this adverse effect.1 During the open-label trial, this type of reaction seemed to diminish over time.6
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Commentary:

Laronidase is the first enzyme replacement therapy marketed for use in the treatment of MPS I. Given the lack of treatment alternatives for this debilitating disease, laronidase will be perceived as an attractive option. With the spectrum of severity in MPS I, this agent’s place where it will be of most value needs to be elucidated, particularly in comparison to BMT. It is assumed that central nervous system (CNS) decline is not amenable to this treatment. The clinical data do not allow us to predict the overall effect of long-term use of this medication. Those who choose to adopt this potentially expensive technology will need to consider the future value of additional information from patient registries and post-marketing studies.

References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada. These summaries have not been externally peer reviewed.

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