# PRIOR AUTHORIZATION POLICY

**POLICY:** Neurology – Gene Therapy – Lenmeldy Prior Authorization Policy
- Lenmeldy™ (atidarsagene autotemcel intravenous infusion – Orchard)

**REVIEW DATE:** 05/15/2024

## OVERVIEW

Lenmeldy, an autologous hematopoietic stem cell (HSC)-based gene therapy, is indicated for the treatment of pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ), or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD) in children.[1]

Lenmeldy is given as a one-time (per lifetime) single dose by intravenous infusion.[1] The minimum recommended dose of Lenmeldy is based on the MLD disease subtype and is 4.2 x $10^6$ cluster of differentiation 34+ (CD34+) cells/kg, 9 x $10^6$ CD34+ cells/kg, and 6.6 x $10^6$ CD34+ cells/kg for patients with PSLI, PSEJ, and ESEJ MLD, respectively; the maximum recommended dose for all disease subtypes is 30 x $10^6$ CD34+ cells/kg. The entire treatment process involves several steps. Lenmeldy is prepared from the child's own HSCs, which are collected via mobilization and apheresis procedures. This process takes one or more days to collect an adequate amount of stem cells to manufacture Lenmeldy. The collected stem cells are sent to a manufacturing site and are used to make Lenmeldy; this takes 5 to 6 weeks. Prior to receipt of Lenmeldy, chemotherapy (with busulfan) is given for a few days in a qualified treatment center to prepare the bone marrow to accept the new cells. Following completion of myeloablative conditioning, a minimum of 24 hours of washout must occur before infusion of Lenmeldy. After the Lenmeldy infusion, the child remains in the qualified treatment center for 4 to 12 weeks to monitor recovery. The gene therapy is transduced with a lentiviral vector encoding the human arylsulfatase A (*ARSA*) gene. The agent adds functional copies of the *ARSA* gene into the child's own HSCs.

The safety and effectiveness of Lenmeldy have been established in children with PSLI, PSEJ, and ESEJ MLD.[1] The clinical trial involving Lenmeldy treated 20 children with PSLI, 7 children with PSEJ, and 10 children with ESEJ MLD; children were between the ages of 8 months and 19 months (median age of 12 months), 11 months to 5.56 years (median age of 2.57 years), and 2.54 years to 11.64 years (median age of 5.84 years), respectively. The safety and efficacy of Lenmeldy have not yet been established in children with the late juvenile form of the disease.

### Disease Overview

MLD is a rare, inherited, autosomal recessive, neurodegenerative lysosomal storage disease caused by deficiency of *ARSA*, due to mutations in the *ARSA* gene.[2-4] MLD is estimated to impact one in every 40,000 individuals in the US. Reduced *ARSA* activity in patients with MLD (usually 0% to less than or equal to 13%) results in accumulation of sulfatides in the central nervous system and peripheral nervous system, leading to progressive demyelination, neuroinflammation, and neurodegeneration. These events lead to progressive motor and cognitive deterioration. Sulfatides also accumulate in visceral organs, such as the gallbladder and kidneys, and cause a host of systemic manifestations as well. The clinical spectrum of MLD is broad and heterogeneous. Defined clinical forms are commonly described on the basis of age at first symptom onset: late-infantile (≤ 30 months of age), juvenile (subdivided into early juvenile [30 months to < 7 years of age] and late juvenile [7 to 16 years of age]), and adult (≥ 17 years of age), with earlier age at onset or the presence of motor symptoms as initial disease manifestations associated with a more severe and rapid disease course. Regardless of the clinical variant, the underlying disease pathophysiology is similar for all phenotypic forms of MLD. Patients with MLD gradually lose the ability to move, talk, swallow, eat, and see. Early mortality is noted.

## Clinical Efficacy

The efficacy of Lenmeldy was evaluated in 39 children that involved two single-arm, open-label clinical trials, as well as a European Union (EU) expanded access program.[1,5] The data involved 20 children with PSLI, 7 children with PSEJ, and 10 children with ESEJ MLD.[1] All children had biochemical and molecular diagnosis of MLD based on *ARSA* activity below the normal range, as well as the presence of two disease-causing *ARSA* alleles. A 24-hour urine collection was required to show elevated sulfatide levels in selected patients. The main efficacy outcomes with Lenmeldy involved motor and neurocognitive function, as evaluated by gross motor function classification for metachromatic leukodystrophy (GMFC-MLD) levels and standard scores on age-appropriate neurocognitive tests, respectively. Comparisons with Lenmeldy were made with an external untreated natural history cohort of children with late juvenile (n = 28) and early juvenile (n = 21) MLD; data were collected retrospectively and prospectively. The primary endpoint was severe motor impairment-free survival, defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (GMFC-MLD Level $\geq 5$) or death. Treatment with Lenmeldy significantly extended severe motor impairment-free survival in children with PSLI MLD vs. the untreated late infantile natural history children. Patients given Lenmeldy had significantly extended severe motor impairment-free survival in this population compared with untreated late infantile natural history children. Seventeen children with PSLI MLD treated with Lenmeldy have been followed until at least the age of 5 years; all children given Lenmeldy remained event-free compared with none of the untreated children in the late infantile natural history group. In total, 14 children treated with Lenmeldy and 24 children from the natural history group had adequate follow-up to determine survival at 6 years from birth. At this timepoint, all children who had PSLI and were treated with Lenmeldy were alive vs. only 58% of children in the late infantile natural history group. In children with PSEJ and ESEJ MLD, those given Lenmeldy displayed slowing of motor and/or cognitive function. It is notable that retention of cognitive function usually does not occur in patients with early juvenile MLD; motor and cognitive functioning typically decline in tandem in children who are not treated.

## Guidelines

A consensus guideline for the monitoring and management of MLD in the US was released in April 2024.[2] In early-onset MLD, including late infantile and early juvenile subtypes, gene therapy (Lenmeldy) should be considered for presymptomatic patients where available. In late-onset MLD, including late juvenile and adult subtypes, HSC transplant (allogeneic) should be considered for patients with no or minimal disease involvement.

## POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lenmeldy. Approval is recommended for those who meet the Criteria for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lenmeldy as well as the specialized training required for administration of Lenmeldy, approval requires Lenmeldy to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate timeframe to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by the Medical Director as noted by **[verification required]**.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with EviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc

Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

**Documentation:** Documentation is required for use of Lenmeldy as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lenmeldy is recommended in those who meet the following criteria:

### FDA-Approved Indication

1. **Metachromatic Leukodystrophy.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, and J).
   - **A)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has presymptomatic late infantile (PSLI) metachromatic leukodystrophy (MLD) and meets ALL of the following (a, b, and c):
       - **a)** Patient has an arylsulfatase A (*ARSA*) genotype consistent with presymptomatic late infantile MLD **[documentation required]**; AND
       - **b)** The disease onset was at ≤ 30 months of age; AND
       - **c)** According to the prescribing physician, the patient is presymptomatic; OR
         Note: Presymptomatic status is defined as the absence of neurological signs and symptoms of MLD. However, presymptomatic children are allowed to have abnormal reflexes or abnormalities on brain magnetic resonance imaging and/or nerve conduction tests not associated with functional impairment (e.g., no tremor, no peripheral ataxia).
     - **ii.** Patient has presymptomatic early juvenile (PSEJ) metachromatic leukodystrophy (MLD) and meets ALL of the following (a, b, and c):
       - **a)** Patient has an arylsulfatase A (*ARSA*) genotype consistent with presymptomatic early juvenile MLD **[documentation required]**; AND
       - **b)** The disease onset was between > 30 months and < 7 years of age; AND
       - **c)** According to the prescribing physician, the patient is presymptomatic; OR
         Note: Presymptomatic status is defined as the absence of neurological signs and symptoms of MLD or physical examination findings limited to abnormal reflexes and/or clonus. However, presymptomatic children were allowed to have abnormal reflexes or abnormalities on brain magnetic resonance imaging and/or nerve conduction tests not associated with functional impairment (e.g., no tremor, no peripheral ataxia).
     - **iii.** Patient has early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD) and meets ALL of the following (a, b, and c):
       - **a)** Patient has an arylsulfatase A (*ARSA*) genotype consistent with early symptomatic early juvenile MLD **[documentation required]**; AND
       - **b)** The disease onset was between > 30 months and < 7 years of age; AND
       - **c)** The patient has early symptomatic status by meeting BOTH of the following [(1) and (2)]:
         - **(1)** Patient is walking independently as defined as being at gross motor function classification for metachromatic leukodystrophy [GMFC-MLD] Level 0 (with or without ataxia) or GMFC-MLD Level 1; AND
         - **(2)** Patient has an intelligence quotient ≥ 85; AND
   - **B)** Patient has not received Lenmeldy in the past **[verification in claims history required]**; AND

Note: If no claim for Lenmeldy is present (or if claims is not available), the prescribing physician confirms that the patient has not previously received Lenmeldy.

**C)** Patient has low arylsulfatase A (*ARSA*) activity indicative of metachromatic leukodystrophy (MLD) **[documentation required]**; AND
Note: Normal laboratory reference range for *ARSA* activity in the peripheral blood mononuclear cells is 31 to 198 nmol/mg/hour. In patients with MLD, *ARSA* activity is 0% to less than or equal to 13%.

**D)** Patient has elevated sulfatide levels above the normal laboratory reference range as evaluated by 24-hour urine collection **[documentation required]**; AND

**E)** According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND

**F)** According to the prescribing physician, patient meets ALL of the following (i, ii, and iii):
- **i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
- **ii.** A granulocyte-colony stimulating factor product with or without a hematopoietic stem cell mobilizer will be utilized for mobilization; AND
  Note: Filgrastim products are examples of a granulocyte-colony stimulating factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
- **iii.** Busulfan will be used for myeloablative conditioning; AND

**G)** Prior to collection of cells for manufacturing, cellular screening is negative for ALL of the following (i, ii, iii, iv, v, and vi):
- **i.** Human immunodeficiency virus (HIV)-1 and HIV-2 **[documentation required]**; AND
- **ii.** Hepatitis B virus **[documentation required]**; AND
- **iii.** Hepatitis C virus **[documentation required]**; AND
- **iv.** Human T-lymphotrophic virus (HTLV)-1 and HTLV-2 **[documentation required]**; AND
- **v.** Cytomegalovirus **[documentation required]**; AND
- **vi.** Mycoplasma **[documentation required]**; AND

**H)** The medication is prescribed by a hematologist, a neurologist, a medical geneticist physician, or a stem cell transplant specialist physician; AND

**I)** Current patient body weight has been obtained within 30 days **[documentation required]**; AND

**J)** If criteria A through I are met, approve one dose of Lenmeldy by intravenous infusion to provide a one-time (per lifetime) single dose within the following dosing ranges according to ONE of the following metachromatic leukodystrophy (MLD) disease types (i, ii, or iii):
- **i.** For presymptomatic late infantile MLD, the minimum recommended dose is $4.2 \times 10^6$ CD34+ cells/kg up to a maximum recommended dose of $30 \times 10^6$ CD34+ cells/kg **[verification required]**; OR
- **ii.** Presymptomatic early juvenile MLD, the minimum recommended dose is $9 \times 10^6$ CD34+ cells/kg up to a maximum recommended dose of $30 \times 10^6$ CD34+ cells/kg **[verification required]**; OR
- **iii.** Early symptomatic early juvenile MLD, the minimum recommended dose is $6.6 \times 10^6$ CD34+ cells/kg up to a maximum recommended dose of $30 \times 10^6$ CD34+ cells/kg **[verification required]**.

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lenmeldy is not recommended in the following situations:

1. **Late Juvenile Form of Metachromatic Leukodystrophy.** The safety and efficacy have not yet been established in children with the late juvenile form of the disease.[1]

2. **Adult Form of Metachromatic Leukodystrophy.** The safety and efficacy have not yet been established in patients with the adult form of the disease.

3. **Gross Motor Function Classification for Metachromatic Leukodystrophy (GMFC-MLD) > Level 1.** These patients were not included in the clinical studies.

4. **Prior Allogeneic Hematopoietic Stem Cell Transplantation in the Past 6 Months or Evidence of Residual Donor Cells.**
   Note: Prescribing physician must confirm that the patient has not received a prior allogeneic hematopoietic stem cell transplantation in the past 6 months.
   Prior allogeneic hematopoietic stem cell transplant within the past 6 months prevented participation, as well as evidence of residual donor cells in those who had underdone allogeneic hematopoietic stem cell transplantation.

5. **Prior Receipt of Gene Therapy.** Lenmeldy has not been studied in a patient who has received prior gene therapy.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Lenmeldy™ intravenous infusion [prescribing information]. Boston, MA: Orchard; March 2024.
2. Adang LA, Bonkowsky JL, Boelens JJ, et al. Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States. *Cytotherapy*. 2024 Apr 1:S1465-3249. [Online ahead of print].
3. Gomez-Ospina N. Arylsulfatase A Deficiency. 2006 May 30 [Updated 2024 Feb 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1130/pdf/Bookshelf_NBK1130.pdf. Accessed on May 9, 2024.
4. FDA News Release. FDA approved first gene therapy for children with metachromatic leukodystrophy. March 18, 2024. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-children-metachromatic-leukodystrophy. Accessed on May 9, 2024.
5. Fumagalli F, Calbi V, Sora MGN, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase I/II trial and expanded access. *Lancet*. 2022;399:372-383.