Drug Coverage Policy

Effective Date……06/05/2025
Coverage Policy Number……IP0695
Policy Title……Lenmeldy

Neurology – Gene Therapy – Lenmeldy

- Lenmeldy™ (atidarsagene autotemcel intravenous infusion - Orchard)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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 cycles 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 to prepare the bone marrow to accept the modified cells. Following completion of myeloablative conditioning, a minimum of 24 hours of washout must occur before infusion of Lenmeldy. 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. 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.[2-5] MLD is estimated to impact one in every 40,000 individuals in the US.[4] 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.[2] 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.[2,3] Defined clinical forms are commonly described mainly on the basis of age at first symptom onset: late-infantile (≤ 30 months of age [50% to 60% of patients]), juvenile (subdivided into early juvenile [30 months to < 7 years of age] and late juvenile [7 to 16 years of age] {20% to 40% of patients}), and adult (≥ 17 years of age [10% to 20% of patients]), with earlier age at onset or the presence of motor symptoms as initial disease manifestations associated with a more severe and rapid disease course.[2-4] 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] Biochemical and molecular diagnosis of MLD was required which included *ARSA* activity below the normal range and 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.[1] 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 ≥ 5) or death.[1,5] The GMFC-MLD

scale evaluated gross motor function in those with MLD and ranges from Level 0 (normal function) to Level 6 (loss of all gross motor function).[5] GMFC-MLD levels are described in Table 1.

Table 1. GMFC-MLD Levels.[5]

Level	Description
Level 0	Walking without support with quality of performance that is normal for age.
Level 1	Walking without support but with reduce quality of performance (i.e., instability when standing or walking).
Level 2	Walking with support. Walking without support is not possible (fewer than five steps)
Level 3	Sitting without support and locomotion such as crawling or roiling. Walking with or without support is not possible.
Level 4	Either sitting without support but no locomotion OR sitting without support not possible but locomotion such as crawling or rolling.
Level 5	No locomotion nor sitting without support but head control is possible.
Level 6	Loss of any locomotion as well as loss of any head and trunk control.

GMFC-MLD – Gross motor function classification for metachromatic leukodystrophy.

The key published study with Lenmeldy, which involves most patients previously detailed, showed that after a follow-up of around 6.7 years, there was a significantly lower risk of severe motor impairment (GMFC-MLD level ≥ 5) or death compared with no treatment among patients with PSLI, PSEJ, and ESEJ MLD.[5] The percentage of patients surviving without severe cognitive impairment was also much higher for patients given Lenmeldy compared with those not receiving this gene therapy.

Guidelines

A consensus guideline for the monitoring and management of MLD in the US was published in 2024.[2] The diagnosis of MLD should include both genetic and biochemical testing (enzyme activity and sulfatide levels). 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.

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for benefit coverage of Lenmeldy. Approval is recommended for those who meet the **Criteria** and **Dosing** 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 a Medical Director as noted by **[verification required]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

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.

Lenmeldy is considered medically necessary when the following criteria are met:

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, J and K):
   - **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 history 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 will have discontinued from anti-retrovirals (prophylactic for human immunodeficiency virus) for at least 1 month prior to mobilization; AND

Note: Examples of anti-retrovirals include abacavir, emtricitabine, lamivudine, and zidovudine.

G) 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

H) Patient 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

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

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

K) If criteria A through J 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 4.2×10^6 CD34+ cells/kg of body weight up to a maximum recommended dose of 30×10^6 CD34+ cells/kg of body weight **[verification required]**; OR
- **ii.** Presymptomatic early juvenile MLD, the minimum recommended dose is 9×10^6 CD34+ cells/kg of body weight up to a maximum recommended dose of 30×10^6 CD34+ cells/kg of body weight **[verification required]**; OR
- **iii.** Early symptomatic early juvenile MLD, the minimum recommended dose is 6.6×10^6 CD34+ cells/kg of body weight up to a maximum recommended dose of 30×10^6 CD34+ cells/kg of body weight **[verification required]**.

Dosing. The recommended dose of Lenmeldy is one dose given 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 (A, B, or C):

A) For presymptomatic late infantile MLD, the minimum recommended dose is 4.2 x 10^6 CD34+ cells/kg of body weight up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg of body weight **[verification required]**; OR

B) Presymptomatic early juvenile MLD, the minimum recommended dose is 9 x 10^6 CD34+ cells/kg of body weight up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg of body weight **[verification required]**; OR

C) Early symptomatic early juvenile MLD, the minimum recommended dose is 6.6 x 10^6 CD34+ cells/kg of body weight up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg of body weight **[verification required]**.

Conditions Not Covered

Lenmeldy for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J3391	Injection, atidarsagene autotemcel, per treatment (Code Effective 7/1/2025)
J3590	Unclassified biologics (Code Effective Until 6/30/2025)

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;26(7):739-748.
3. Gomez-Ospina N. Arylsulfatase A Deficiency. 2006 May 30 [Updated 2024 Apr 25]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1130/pdf/Bookshelf_NBK1130.pdf. Accessed on May 19, 2025.
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 19, 2025.
5. Fumagalli F, Calbi V, Gallo V, et al. Long-term effects of atidarsagene autotemcel for metachromatic leukodystrophy. *N Engl J Med*. 2025;392(16):1609-1620.

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy	08/15/2024
Selected Revision	**Updated HCPCS Coding** **Added** HCPCS code: • J3391 (Codes Effective 7/1/2025) **Updated** the description for J3590 to include the note "Code effective until 6/30/2025	5/15/2025
Annual Revision	**Metachromatic Leukodystrophy:** The following requirement was added, "according to the prescribing physician, the patient will have discontinued from anti-retrovirals (prophylactic for human immunodeficiency virus [HIV]) for at least 1 month prior to mobilization". A Note was added that examples of anti-retrovirals include abacavir, emtricitabine, lamivudine, and zidovudine. The qualifier "Prior to collection of cells for manufacturing" as well as the word "cellular" was removed from the requirement regarding screening for certain viruses and the word "Patient" was added. The criterion now reads: "Patient screening is negative for ALL of the following...." Regarding dosing, the phrase "of body weight" was added after the cited dosing which is in units of cells/kg. The phase "the past" was added before the criterion regarding body weight which now states that "Current patient body weight has been obtained within the past 30 days".	6/5/2025

The policy effective date is in force until updated or retired.