MEDICAL COVERAGE POLICY	
SERVICE:	**Atidarsagene autotemcel (Lenmeldy™)**
Policy Number:	**309**
Effective Date:	**05/01/2025**
Last Review:	**04/14/2025**
Next Review:	**04/14/2026**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Atidarsagene autotemcel (Lenmeldy™)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

Baylor Scott & White Health Plan (BSWHP) may consider atidarsagene autotemcel (Lenmeldy™) medically necessary for the treatment of metachromatic leukodystrophy (MLD) in pediatric patients when ALL of the following criteria are met:

1. Member has diagnosis of metachromatic leukodystrophy (MLD) as evidenced by **ALL** of the following criteria:
    a. ARSA activity below the normal range in peripheral blood mononuclear cell or fibroblasts evaluation **AND**
    b. Presence of sulfatides in 24-hour urine collection to exclude MLD carriers and patients with ARSA pseudo-deficiency

    AND
2. Member has diagnosis meeting the criteria for one of the following forms of MLD:
    a. Pre symptomatic late infantile (PSLI) as defined by all of the following:
        i. ARSA genotype consistent with late infantile MLD (i.e. two null mutant ARSA alleles) **AND**
        ii. Pre-symptomatic clinical status at time of treatment defined as absence of neurological impairment (disease-related symptoms), with or without signs of the disease revealed by instrumental evaluations (electroneurographic and brain magnetic resonance imaging)
    b. Early juvenile with all of the following:

i. ARSA genotype consistent with early juvenile MLD (i.e. one null and one residual mutant *ARSA* allele) **AND**
ii. One of the following:
    1. Pre symptomatic defined as the absence of neurological signs and symptoms of MLD or physical exam findings limited to abnormal reflexes and/or clonus **OR**
    2. Early symptomatic as defined by presence of neurological signs and symptoms of MLD **AND** intelligence quotient ≥85 **AND** retaining the ability to walk independently for ≥10 steps **AND** age less than 7 years at time of symptom onset

AND

3. The medication is prescribed by or in consultation with a pediatric neurologist or specialist in MLD **AND**
4. Member has been assessed to be an appropriate candidate for apheresis **AND**
5. Member will be receiving atidarsagene autotemcel at a certified treatment center **AND**
6. Member does **NOT** have any of the following:
    a. Positive screening for hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus 1 & 2 (HTLV-1/HTLV-2), human immunodeficiency virus 1 & 2 (HIV-1/HIV-2), cytomegalovirus (CMV), and/or mycoplasma infection
    b. Recent anti-retroviral medication use (within the time needed for expected total elimination of medication **OR** 30 days, whichever is longer)
    c. Hematopoietic stem cell transplant within previous 6 months or evidence of residual cells of donor origin
    d. Affected by neoplastic diseases (i.e. myelodysplastic syndrome or acute myelogenous leukemia AML)
    e. Previous atidarsagene autotemcel treatment
    f. Diagnosis of early symptomatic late infantile, late juvenile, or adult MLD
    g. Entering MLD rapid phase of decline as evidenced by the loss of the ability to walk

BSWHP considers repeat administration of atidarsagene autotemcel experimental and investigational because the effectiveness of this strategy has not been established.

BSWHP considers atidarsagene autotemcel for the treatment of all other indications to be experimental and investigational because the effectiveness of this strategy has not been established.

All requests will be reviewed by a clinical pharmacist and medical director.

BACKGROUND:

Metachromatic leukodystrophy (MLD) is a neurodegenerative lysosomal storage disease that causes progressive cognitive and motor impairment. Lysosomal storage diseases are inherited disorders characterized by disruption of enzymes involved with a host of normal cellular maintenance processes.

This leads to an accumulation of molecules within the cells, which ultimately leads to cell death. MLD is caused by a defect in the arylsulfatase A (ARSA) lysosomal enzyme resulting from a mutation in the *ARSA* gene. Defect in the ARSA enzyme leads to an accumulation of sulfatides in cells, which is toxic. Excessive sulfatide levels destroy the myelin producing cells, thereby impacting the myelin sheaths of the peripheral and central nervous systems. Sulfatides also accumulate in gallbladder, kidneys, and testes.

MLD is the most common leukodystrophy and has a worldwide prevalence rate of 40,000 to 160,000. Certain populations have a higher incidence of MLD, including Habbanite (1 in 75), Navajo (1 in 2500), and Israeli Arab people (1 in 8000). The incidence of MLD in the United States is estimated at 1 in 40,000.

The diagnosis of MLD is based upon clinical manifestations, genetic analysis, magnetic resonance imaging (MRI) of the brain, and biochemical testing for ARSA enzyme activity.

The manifestation of MLD is related to the progressive cognitive and motor impairment caused by the damaged myelin sheaths. MLD is categorized according to the age of onset, each of which has different clinical presentations:

Late infantile (50% to 60% of cases)
- Onset < 30 months of age
- The most severe form of MLD
- Early milestones are met followed by progressive loss of motor skills, hypotonia, spasticity, dysarthria, ataxia, hyporeflexia, optic atrophy, and extensor plantar posturing
- Death occurs during childhood

Juvenile (20% to 30% of cases)
- Onset between 30 months of age and puberty
- Heterogenous presentation
- Early milestones are met followed by intellectual decline, psychomotor regression, personality changes, behavioral issues, ataxia, peripheral neuropathy, dementia, optic atrophy, memory loss, and impulsiveness
- Death occurs within a few years of symptom onset; however, patients receiving supportive treatment may survive years in a vegetative state

Adult (15% to 20% of cases)
- Late adolescence to adulthood onset
- Neurocognitive and neuropsychiatric difficulties, including peripheral neuropathy, schizophrenia, psychosis, seizures, depression, mood swings, dementia, memory loss, and impulsiveness

- Minimal or no impact on motor function
- Death occurs approximately 20 to 30 years after symptom onset

There is no cure for MLD, and treatment consists of managing symptoms to improve quality of life. In some cases of late infantile MLD, bone marrow transplantation has delayed progression of the disease. Atidarsagene autotemcel (Lenmeldy; Orchard Therapeutics) is the first disease-modifying therapy approved in the United States for treatment of MLD and was developed to address the underlying cause of the disorder. It received FDA approval on March 18, 2024 but has been approved for use by the European Medicines Agency (EUA) since December 13, 2020.

Atidarsagene autotemcel is a gene therapy containing autologous hematopoietic stem and progenitor cells (HSPCs) that have been transduced with a lentivirus vector containing the human arylsulfatase A (ARSA) gene. The HSPCs are isolated from bone marrow or from mobilized peripheral blood enriched for CD34+ cells through apheresis. A minimum of 8-10 × 106 cells/kilogram (kg) are needed to manufacture the gene therapy. The resulting genetically modified HSPCs are able to synthesize functional ARSA enzymes.

Prior to infusion of atidarsagene autotemcel, the patient undergoes myeloablative conditioning to remove the native HSPCs that carry the defective *ARSA* gene. Treatment consists of a single intravenous infusion of atidarsagene autotemcel. The genetically modified HSPCs are able to repopulate the hematopoietic space. Certain populations of the genetically modified blood cells are able to cross the blood-brain barrier to engraft in the central nervous system. It is anticipated that successful and stable engraftment of the genetically modified cells should produce a persistent therapeutic effect.

The available evidence evaluating atidarsagene autotemcel for the treatment of metachromatic leukodystrophy (MLD) is limited to 3 publications reporting on a phase I/II trial (NCT01560182), including long-term results of 29 patients 1 initial report of the first few patients enrolled, and 1 ad-hoc analysis of 9 patients with ≥ 18 months of follow-up.

In the phase I/II single-arm trial with expanded access, 29 pediatric patients with late infantile (n=16; mean age, 12.8 months; pre-symptomatic, 94%) or early juvenile (n=13; mean age, 65.9 months; pre-symptomatic, 38%) MLD received a single intravenous infusion of atidarsagene autotemcel. Prior to infusion, patients were treated with busulfan at a target cumulative area under the curve of 67.2 milligrams (mg) × hours/liter (h/L) (sub myeloablative; first 13 patients) or 85.0 mg × h/L (myeloablative, patients 14-29).

The coprimary endpoints were a > 10% improvement in total score of the 88-item gross motor function measure (GMFM-88) at 2 years compared with historical matched controls and the change in peripheral blood mononuclear cell (PBMC) ARSA activity from baseline to 2 years.

The median follow-up was 3.16 years (range, 0.64 to 7.51). Hematological engraftment was confirmed in all patients. The mean ARSA activity in PBMCs increased from baseline by a mean of 18.7 times (95% CI, 8.8 to 42.2; *P*<0.0001) in patients with late infantile MLD and 5.7 times (95% CI, 2.6 to 12.4; *P*<0.0001) in patients with early juvenile MLD. ARSA activity in PBMCs remained stable during follow-up. The mean ARSA activity in cerebral spinal fluid was not detectable at baseline, above measurable levels at 3 months, attained normal levels by 6 to 12 months, and remained within normal levels during follow-up.

The mean difference in GMFM-88 scores between study patients and matched historical controls at 2 years was greater than the predefined minimum threshold for clinically meaningful efficacy of 10% for 66% (95% CI, 48.9 to 82.3) of patients with late infantile MLD and 42% (95% CI, 12.3 to 71.8) of patients with early juvenile MLD. For 25 of 29 patients, gross motor development was either similar to or slightly worse than healthy children or was stabilized or had a delayed rate of decline compared with the matched historical controls.

There were 3 deaths among the study population, all of which were considered unrelated to atidarsagene autotemcel. Two patients with early juvenile MLD died at 8 and 15 months after treatment, which were attributed to rapid disease progression. The third death was a patient with early juvenile MLD who had a fatal ischemic stroke following an infection 13 months after treatment.

Long-term results of 39 patients with late infantile (n=19) or early juvenile (n=20) MLD who were treated with atidarsagene autotemcel were presented at the WORLDSymposium 2023. The median follow-up was 6.15 years (range, 0.64 to 11.03 years). All patients exhibited normal or above normal levels of ARSA activity in the hematopoietic system within 3 months and in cerebrospinal fluid by 3 to 12 months after treatment. ARSA levels were sustained throughout the follow-up period. When compared with historical controls, the risk of severe motor impairment or death was significantly reduced following treatment with atidarsagene autotemcel. There were no serious adverse events, malignancies, replication-competent lentivirus, or abnormal clonal expansion.

The United Kingdom's National Institute for Health and Care Excellence (NICE) published guidance for atidarsagene autotemcel for treating MLD in 2022. NICE recommends atidarsagene autotemcel for treating MLD with ARSA gene mutations for the following populations:

1. "[F]or children who have late infantile or early juvenile types, with no clinical signs or symptoms."

2. "[F]or children who have the early juvenile type, with early clinical signs or symptoms, and who can still walk independently and have no cognitive decline."

The Institute for Clinical and Economic Review (ICER) published the following final evidence report on atidarsagene autotemcel for MLD on October 30, 2023.

1. "Given that the early onset forms of MLD are rapidly progressive and fatal, and the majority of PSLI and PSEJ MLD patients who underwent treatment remained either asymptomatic or with mild symptoms, we conclude that in children with PSLI and PSEJ MLD, we have high certainty of a substantial net health benefit ("A")."

2. "The magnitude of benefit and certainty in that benefit are both smaller for treatment of children with ESEJ-MLD. These children will not return to normal health, treatment with busulfan carries a risk of death, long-term outcomes are less certain. Additionally, clinical experts, based on experience in patients treated with hematopoietic stem cell therapy, were concerned that, in some patients, treatment may carry the risk of hastening progression of physical and cognitive decline before stabilization occurs. Given these uncertainties, in children with early symptomatic EJ-MLD, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit ("B+")."

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	96365 - Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour 96366 - Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure) 96413 - Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug 96415 - Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)
HCPCS Codes:	C9399 - (unclassified drugs or biologicals, hospital outpatient use) J3590 - (unclassified biologics)
ICD10 codes:	E75.25 - Metachromatic leukodystrophy
ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	6/10/2024	New policy

Updated	04/14/2025	Formatting changes, updated ending note sections to align with CMS requirements and business entity changes.

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

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2. Fumagalli F, Calbi V, De Mattia F, et al. Long-term clinical outcomes of atidarsagene autotemcel (autologous hematopoietic stem cell gene therapy [HSC-GT] for metachromatic leukodystrophy) with up to 11 years follow-up. *Mol Genet Metab.* 2023;138(2). doi:10.1016/j.ymgme.2022.107108
3. Fumagalli F, Calbi V, Natali Sora MG, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. *Lancet.* 2022;399(10322):372-383. doi:10.1016/s0140-6736(21)02017-1
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7. Lenmeldy [package insert]. Boston, MA: Orchard Therapeutics; 2024
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9. Fumagalli F, Zambon AA, Rancoita PMV, Baldoli C, Canale S, Spiga I, et al. Metachromatic leukodystrophy: a single-center longitudinal study of 45 patients. J Inherit Metab Dis. 2021;1-14.
10. MacFaul R, Cavanagh N, Lake BD, Stephens R, Whitefield AE. Metachromatic leukodystrophy: review of 38 cases. Arch Dis Child. 1982;57:168-175.
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12. National Institute for Health and Care Excellence. (2022). Atidarsagene autotemcel for treating metachromatic leukodystrophy. [NICE Guideline No. HST18]. https://www.nice.org.uk/guidance/hst18
13. European Medicine Agency. (2023). Libmeldy. https://www.ema.europa.eu/en/medicines/human/EPAR/libmeldy
14. Institute for clinical and economic review. (2023). Atidarsagene autotemcel for metachromatic leukodystrophy: final policy recommendations. https://icer.org/wp-content/uploads/2023/10/ICER_MLD_2023_Policy-Recommendations_10302023.pdf
15. IPD Analytics. (2024). Lenmeldy (atidarsagene autotemcel) suspension for intravenous infusion by Orchard Therapeutics.

***Note**:*

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Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid is offered through Scott and White Health Plan in the Central Texas Medicaid Rural Service Area (MRSA); FirstCare STAR is offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs; and FirstCare CHIP is offered through FirstCare in the Lubbock Service Area.