BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 05/16/24**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE:**
	CURRENT EFFECTIVE DATE: 05/16/24
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 2ND QTR 2025	**ARCHIVE DATE:**

GENE THERAPY FOR METACHROMATIC LEUKODYSTROPHY

- **LENMELDY (atidarsagene autotemcel)**

Non-Discrimination Statement is located at the end of this document.
Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for initial therapy:** Lenmeldy (atidarsagene autotemcel) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in or in consultation with a specialist in metachromatic leukodystrophy such as a Pediatric Neurologist

2. Individual is 6 years of age or younger at the time of infusion

3. Individual has a confirmed diagnosis of pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD) with documentation of **BOTH** of the following:

   - Arylsulfatase A (ARSA) activity is below the normal range
   - **ONE** of the following:

     a. Biallelic pathogenic variant in the ARSA gene (e.g., 0/0, 0/R)
     b. Elevated sulfatide levels from 24-hour urine collection

4. Individual meets **ONE** of the following:

   - Diagnosis of PSLI or PSEJ with **ALL** of the following

     a. Diagnosis secondary to affected sibling or newborn screening
     b. Expected disease onset is ≤ 6 years of age (e.g., genotype 0/0, genotype 0/R or sibling onset is ≤ 6 years of age)
     c. Absence of neurological signs and symptoms of MLD associated with cognitive, motor, or behavioral functional impairment or regression

   - Diagnosis of ESEJ meets **ALL** of the following:

     a. Symptoms onset was between > 30 months and ≤ 6 years of age
     b. Gross Motor Function Classification in MLD (GMFC-MLD) is 0-1 (see Definitions section)
     c. Intelligence quotient (IQ) ≥ 85

5. Individual does **NOT** have **ANY** of the following:

   - Active clinically significant infection, including but not limited to HIV, hepatitis B or C, bacteria, viral, fungal, parasitic infections
   - HIV anti-retroviral medications for prophylaxis 1 month prior to mobilization
   - Prior gene therapy or is being considered for treatment with any other gene therapy

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- Prior allogenic hematopoietic stem cell transplant in the past 6 months

Approval duration: One-time treatment per lifetime
The safety and effectiveness of repeat administration of Lenmeldy (atidarsagene autotemcel) have not been evaluated.

Approval conditions:
If an individual meets all coverage guideline criteria and is approved to receive treatment, the requesting provider and/or referring provider attests and agrees to submit clinical outcomes data and information.

- Lenmeldy (atidarsagene autotemcel) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include*, but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.
- Symptomatic infantile MLD
- Late juvenile MLD
- Adult MLD

Attestations for Lenmeldy

Physician Name: _____

Individual Name: _____ DOB**:** _____

- The Physician is responsible for filling out this form. This form may be completed by the physician requesting and administering Lenmeldy or by the referring neurologist who will resume follow-up care for metachromatic leukodystrophy.
- All elements must be initialed, and the form must be signed by the Physician (or designee).
- Incomplete forms will be returned to acquire missing information, initial, signature, or date.

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➢ Return completed form to BCBSAZ.

Physician Agreement:

- Physician to initial by each element and date and sign to show willingness to participate.
- Documentation may include, but is not limited to, chart notes, laboratory test results, claims records, and/or other information.

Initials:

_____ I verify that the patient will be closely followed and monitored for progression of disease

_____ I agree to submit clinical outcomes data and information

Provider (or designee) Signature: _____

Date: _____

Description:

Metachromatic leukodystrophy (MLD) is a rare, autosomal recessive, inherited lysosomal storage disease. The lack of an enzyme called arylsulfatase A (ARSA) leads to the accumulation of sulfatides that causes progressive demyelination of the central and peripheral nervous system.

Lenmeldy (atidarsagene autotemcel) is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) MLD.

Atidarsagene autotemcel inserts one or more functional copies of the human arylsulfatase A (ARSA) complementary deoxyribonucleic acid (cDNA) into the patients' hematopoietic stem cells, through transduction of autologous CD34 cells with ARSA lentiviral vector. After atidarsagene autotemcel infusion, transduced CD34 HSCs engraft in bone marrow, repopulate the hematopoietic compartment and their progeny produce ARSA enzyme. Functional ARSA enzyme can breakdown or prevent the harmful accumulation of sulfatides.
Lenmeldy will be administered at Qualified Treatment Centers (QTC) in the United States and requires an intensive four step process with additional monitoring after administration. Due to the complexity of stem-cell based gene therapy only available at QTCs, care coordination should be considered to assist the member when needed.

- Step 1: Collection of blood stem cells through mobilization and apheresis. This process takes approximately one week. Granulocyte-colony stimulating factor (G-CSF) and plerixafor were used for mobilization.
- Step 2: Blood stem cells are sent to the manufacturing site and the functioning ARSA gene is attached to the stem cells to make Lenmeldy. This step takes approximately 6 to 8 weeks.

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- Step 3: The individual is hospitalized and myeloablative chemotherapy (busulfan) is administered.
- Step 4: Lenmeldy is administered intravenously. The individual remains hospitalized at the QTC during administration and for monitoring afterward for approximately 4 to 12 weeks.

Definitions:

MLD Subtypes and Symptom Level

Late Infantile MLD (LI-MLD)	▪ Symptom onset before 2.5 years of age ▪ Little or no residual ARSA activity ▪ Typically survive 5-7 years post-diagnosis with standard treatment
Early Juvenile MLD (EJ-MLD)	▪ Symptom onset after 2.5 years and before 7 years of age ▪ May survive 10-20 years after diagnosis
Late Juvenile MLD	▪ Symptom onset at 7 years of age to 16 years of age ▪ May survive 10-20 years after diagnosis
Adult MLD	▪ Symptom onset at 17 years of age and older ▪ Slowly progressive and may survive 20 to 30 years after onset
Pre-symptomatic MLD	Defined in trials as patients without disease-related neurological impairments, with or without signs of the disease via electroneurographic and brain MRI
Early symptomatic MLD	Defined in trials as patients with an intelligence quotient of 85 or above with the ability to walk without support but with reduced quality of performance (GMFC-MLD level 0-1)

Gross Motor Function Classification in MLD (GMFC-MLD)

Level 0	Walking without support with quality of performance normal for age
Level 1	Walking without support but with reduced quality of performance, i.e. instability when standing or walking
Level 2	Walking with support. Walking without support not possible (fewer than five steps)
Level 3	Sitting without support and locomotion such as crawling or rolling. Walking with or without support not possible
Level 4	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

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	05/16/24	Approved guideline
Clinical Pharmacist	04/11/24	Development

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Coding:

HCPCS: C9399, J3590

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Resources:

Literature reviewed 05/16/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Bonkowsky JL. Metachromatic leukodystrophy. In: UpToDate, Patterson MC, Firth HV, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated on March 12, 2024. Accessed on April 1, 2024.

2. Lenmeldy (atidarsagene autotemcel) prescribing information, revised by Orchard Therapeutics (Europe) Ltd 03/2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 1, 2024.

3. Lin G, Suh K, Fahim SM, et al. Atidarsagene Autotemcel for Metachromatic Leukodystrophy. Institute for Clinical and Economic Review, October 30, 2023. https://icer.org/assessment/metachromatic-leukodystrophy-2023/#timeline. Accessed on April 1, 2024.

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Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html