atidarsagene autotemcel (Lenmeldy™)

Policy # 00891
Original Effective Date: 11/01/2024
Current Effective Date: 11/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of atidarsagene autotemcel (Lenmeldy™)‡ for the treatment of metachromatic leukodystrophy to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for atidarsagene autotemcel (Lenmeldy) will be considered when all of the following criteria are met:

- Patient has a diagnosis of metachromatic leukodystrophy (MLD) as confirmed by documentation of ALL of the following:
    - Arylsulfatase A (ARSA) enzyme activity below the normal range in peripheral blood mononuclear cells or fibroblasts; AND *(Note: Normal laboratory reference range for ARSA activity in the peripheral blood mononuclear cells is 31 to 190 nmol/mg/hour. In patients with MLD, ARSA activity is 0% to ≤ 13%)*
    - Identification of two known or novel disease-causing *ARSA* alleles; AND
    - If a novel *ARSA* variant(s) is identified, documentation confirming presence of sulfatides in a 24-hour urine collection is submitted; AND
- Patient has one of the following subtypes of MLD based on the below definitions: pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ), or early symptomatic early juvenile (ESEJ):

- Pre-symptomatic late infantile (PSLI):
  - Patient meets TWO of the following:
    - Expected disease onset ≤ 30 months of age based on age at onset of sibling(s)
    - *ARSA* genotype consistent with late infantile MLD (e.g., two null (0) mutant *ARSA* alleles)
    - Peripheral neuropathy as determined by electroneurographic study; AND
  - Patient does not have disease-related symptoms
- Pre-symptomatic early juvenile (PSEJ):
  - Patient meets TWO of the following:
    - Expected age at onset of symptoms (based on older sibling) between 30 months and 6 years
    - One null (0) and one residual (R) mutant *ARSA* allele(s)
    - Peripheral neuropathy as determined by electroneurographic study; AND
  - Patient does not have disease-related symptoms OR has symptoms limited to clonus and/or abnormal reflexes
- Early symptomatic early juvenile (ESEJ):
  - Patient meets TWO Of the following:
    - Age at onset of symptoms between 30 months and 6 years
    - One null (0) and one residual (R) mutant *ARSA* allele(s)
    - Peripheral neuropathy as determined by electroneurographic study; AND
  - Patient has a gross motor function classification for metachromatic leukodystrophy (GMFC-MLD) score of 0 with ataxia or score of 1 with or without ataxia; AND
  - Patient has an intelligence quotient (IQ) ≥ 85 on age-appropriate neurodevelopmental testing

- Patient has not received Lenmeldy previously or any other gene or cell therapy; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- According to the prescribing physician, the patient is a candidate for hematopoietic stem cell transplant; AND

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- Patient has not received a prior allogeneic hematopoietic stem cell transplant (HSCT) in the last 6 months AND there is no evidence of residual donor cells (if prior allogeneic HSCT > 6 months); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has a negative screening for ALL of the following prior to cell collection:
  - Human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2)
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Human T-lymphotropic virus (HTLV-1 and HTLV-2)
  - Cytomegalovirus
  - Mycoplasma; AND
- Lenmeldy will be authorized as one treatment per lifetime; AND
- For PSLI MLD, the minimum recommended dose is 4.2 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg; OR
- For PSEJ MLD, the minimum recommended dose is 9 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg; OR
- For ESEJ MLD, the minimum recommended dose is 6.6 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of atidarsagene autotemcel (Lenmeldy) when the patient has previously received Lenmeldy or any other gene therapy or when the patient has received an allogeneic HSCT in the past 6 months or has residual donor cells from a previous HSCT to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of atidarsagene autotemcel (Lenmeldy) when the patient selection criteria are not met (except those listed above as **not medically necessary****) to be **investigational.***

Background/Overview

Lenmeldy is a gene therapy indicated for the treatment of children with certain forms of metachromatic leukodystrophy (MLD). It is an ex-vivo autologous hematopoietic stem cell gene therapy that uses a lentiviral vector encoding the *ARSA* gene. The stem cells are collected from the patient, modified by adding a functional copy of the *ARSA* gene, and then transplanted back into the patient, where they engraft within the bone marrow. Lenmeldy is intended to be a one-time treatment, administered following conditioning with busulfan. Prior to treatment, patients must undergo HSC mobilization followed by apheresis to obtain CD34+ cells for Lenmeldy manufacturing. Dosing of Lenmeldy is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight with the minimum dose based on the MLD disease subtype.

MLD is a rare, genetic, lysosomal storage disorder caused by deficient activity in the enzyme arylsulfatase A (ARSA). MLD is caused by the accumulation of sulfatides due to ARSA deficiency, which leads to myelin sheath destruction in the nerves of the central and peripheral nervous systems. MLD is a progressive disease with complications including neurocognitive decline, loss of motor function, blindness, peripheral neuropathy, malnutrition, aspiration pneumonia, and eventually death.

There are three types of MLD based on the age at which symptoms appear: late-infantile MLD (6 months to < 30 months of age), juvenile MLD (30 months to 16 years of age, with early juvenile MLD defined as 30 months to < 7 years of age and late-juvenile MLD defined as 7 to < 17 years of age), and adult MLD (17 years of age and older). All MLD subtypes ultimately lead to progressive loss of cognitive and motor function, with the prognosis dependent on the patient's age at diagnosis. The most common subtype is the late-infantile form, in which patients can progress to death within

5 to 6 years of diagnosis. Patients with juvenile MLD generally survive into early adulthood, and adult patients with MLD generally live 10 to 20 years following the onset of symptoms.

Prior to the availability of Lenmeldy, the treatment of MLD was based on symptomatic supportive care to address neurocognitive and neuropsychiatric disturbances (e.g., seizures, spasticity, and feeding problems). Stem cell transplants can be considered but are usually used only in pre-symptomatic or minimally symptomatic children with the juvenile form of MLD.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Lenmeldy was approved in March 2024 for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The safety and efficacy of Lenmeldy was assessed in 39 children across two single-arm, open-label clinical trials and a European Union (EU) expanded access program (EAP). Two children with advanced disease were excluded from the efficacy analysis. The clinical trials enrolled 13 children with PSLI, 6 children with PSEJ, and 9 children with ESEJ MLD. The EU EAP enrolled 7 children with PSLI, 1 child with PSEJ, and 1 child with ESEJ MLD. All children had documented biochemical and molecular diagnosis of MLD based on ARSA activity below the normal range and identification of two disease-causing ARSA alleles. In the case of a novel ARSA variant(s), a 24-hour urine collection was required to show elevated sulfatide levels.

The major efficacy outcomes in clinical trials of Lenmeldy were motor and neurocognitive function, as assessed by GMFC-MLD levels and standard scores on age-appropriate neurocognitive tests, respectively. The efficacy of Lenmeldy was compared to an external untreated natural history (NHx)

cohort of children with LI (n=28) and EJ (n=21) MLD. Data from the NHx cohort were collected both retrospectively and prospectively. Cognitive outcomes in the children with PSEJ and ESEJ MLD were compared to outcomes for untreated children reported in the medical literature.

In clinical trials of Lenmeldy, children were classified as having PSLI, PSEJ, or ESEJ MLD based on the following criteria:

- PSLI MLD: Children with expected disease onset ≤ 30 months and an ARSA genotype consistent with LI MLD. Pre-symptomatic status defined as the absence of neurological signs and symptoms of MLD (except abnormal reflexes or abnormalities on brain magnetic resonance imaging that are not associated with functional impairment).
- PSEJ MLD: Children with expected disease onset > 30 months and < 7 years of age and an ARSA genotype consistent with EJ MLD. Pre-symptomatic status defined as the absence of neurological signs and symptoms of MLD or physical exam findings limited to abnormal reflexes and/or clonus.
- ESEJ MLD: Children with disease onset > 30 months and < 7 years of age and an ARSA genotype consistent with EJ MLD. Early symptomatic status defined as walking independently (GMFC-MLD level 0 with ataxia or GMFC-MLD Level 1) and IQ ≥ 85.

HSCs used for the manufacture of Lenmeldy were obtained by bone marrow collection (n=29), from apheresis collection of peripheral blood following the administration of HSC mobilizing agents (n=8), or both sources (n=2). Mobilization was achieved using G-CSF administered twice daily. From Day 3, plerixafor could be administered once daily. In the clinical trials of Lenmeldy, plerixafor was administered to the 8 children where HSCs were obtained from apheresis collection only. All children received busulfan conditioning with a total dose range of 9 to 32 mg/kg and a target cumulative area under the curve (AUC) of 58,800 to 93,500 µg*h/L. Defibrotide was used in 11/39 children as prophylaxis for vasoocclusive disease (VOD). No additional anti-thrombotic agents were used as prophylaxis for VOD.

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. For analyses of the primary endpoint, an additional 2 untreated siblings not enrolled in the NHx study were included in the comparator group. Treatment with Lenmeldy significantly extended severe motor impairment-free survival in children with PSLI MLD compared with untreated LI natural history children. Seventeen children with PSLI MLD treated with Lenmeldy

have been followed until at least the age of 5 years. At the age of 5 years, 100% of Lenmeldy treated PSLI children remained event-free compared with 0% untreated LI children. Additionally, treatment with Lenmeldy was found to significantly extend overall survival compared to the untreated natural history. Fourteen treated children and 24 natural history children had sufficient follow-up to determine survival at 6 years from birth. At this timepoint, all patients treated with Lenmeldy were alive, and 10 natural history children had died (42%).

Seven children with PSEJ MLD were treated with Lenmeldy. One child died at age 2.1 years from a cerebral infarction. There were insufficient data in three children who were too young at last follow-up to evaluate efficacy of Lenmeldy as symptom onset may not begin until 7 years of age in EJ MLD. Two children had evaluable motor and cognitive outcomes. One child had evaluable motor outcomes, but while showing stable normal cognitive function, was neither old enough nor had sibling data for cognitive events to be evaluable.

Ten patients with ESEJ MLD treated with Lenmeldy had evaluable data. Most had motor disease progression and two patients died. Four children had favorable cognitive outcomes after treatment in the setting of motor decline. Retention of cognitive functioning has not been reported in this phase of EJ MLD disease as motor and cognitive functioning typically decline together in untreated children.

References

1. Lenmeldy [package insert]. Orchard Therapeutics Ltd. Boston, MA. Updated April 2024.
2. Lenmeldy New Drug Review. IPD Analytics. Updated May 2024.

Policy History

Original Effective Date: 11/01/2024
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10/03/2024 Medical Policy Committee review
10/08/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 10/2025

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	N/A
HCPCS	C9399, J3490, J3590
ICD-10 Diagnosis	E75.25

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.