Anthem

Medical Policy

Subject: Gene Therapy for Metachromatic Leukodystrophy
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Description/Scope

This document addresses gene therapy for metachromatic leukodystrophy (MLD), a congenital medical condition that affects the nervous system. MLD is caused by having an abnormal variant of the arylsulfatase A (ARSA) gene, which leads to a deficiency of the enzyme ARSA. Gene therapy for individuals with early onset MLD involves ex vivo transduction of CD34+ cells with a lentiviral vector that contains a working copy of the ARSA gene.

Note: Please see the following related document for additional information:

TRANS.00029 Hematopoietic Stem Cell Transplantation for Genetic Diseases and Aplastic Anemias

Position Statement

Medically Necessary:

A one-time infusion of atidarsagene autotemcel is considered **medically necessary** in individuals who meet **all** of the following criteria:

A. Diagnosis of metachromatic leukodystrophy (MLD); and
B. Documentation of an arylsulfatase A (ARSA) genotype (biallelic ARSA pathogenic variant); **and**
C. One of the following forms of MLD:
    1. Pre-symptomatic[1] late infantile MLD (children with expected disease onset at or before 30 months of age); **or**
    2. Pre-symptomatic[1] early juvenile MLD (children with expected disease onset at more than 30 months and less than 7 years of age); **or**
    3. Early symptomatic[2] early juvenile MLD (children with disease onset at more than 30 months of age and less than 7 years of age): **AND**
D. Biochemical diagnosis of MLD defined by the following:
    1. Deficient ARSA enzyme activity in leukocytes; **and**
    2. Elevated urinary excretion of sulfatides; **and**
E. The individual is a candidate for an allogeneic hematopoietic cell transplantation, but ineligible due the absence of a donor[3]; **and**
F. Alanine transferase (ALT) no more than 2 times upper limit of normal (ULN) or total bilirubin no more than 1.5 ULN; **and**
G. No serious concomitant illness (for example, active malignant neoplasia other than skin cancer, serious hematologic disorder, end-stage organ dysfunction, acute or chronic stable hepatitis B, immunodeficiency disorder, active tuberculosis); **and**
H. No prior gene therapy.

[1] Pre-symptomatic status is defined as the absence of neurological signs and symptoms of MLD or physical exam findings limited to abnormal reflexes and/or clonus. Pre-symptomatic children may have abnormal reflexes or abnormalities on brain magnetic resonance imaging and/or nerve conduction tests not associated with functional impairment.

[2]Early symptomatic status is defined as the ability to walk independently and an intelligence quotient (IQ) greater than or equal to 85.

[3]Documentation that a suitable donor has not been identified, for example, a matched related donor or matched (HLA 8/8 or 7/8) unrelated donor.

Investigational and Not Medically Necessary:

Gene therapy for metachromatic leukodystrophy is considered **investigational and not medically necessary** when the criteria above are not met and in all other situations.

Rationale

Atidarsagene autotemcel (Lenmeldy™, previously known as OTL-200 or arsa-cel) received approval from the Food and Drug Administration (FDA) on March 18, 2024. It is indicated for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) MLD.

FDA approval was based on data on 39 children with MLD who participated in one of two single-arm, open-label studies or in an expanded access program in the European Union (EU). Participants in the clinical trials included 13 children with PSL), 6 children with PSEJ and 9 children with ESEJ MLD. The EU database included 7 children with PSLI, 1 child with PSEJ and 1 child with ESEJ MLD. All participants had documented biochemical and molecular diagnosis of MLD; they had ARSA activity below the normal range and 2 disease-causing ARSA alleles. Outcomes in the treated cohort were compared with data on a separate natural history cohort of children with late infantile (n=28) and early juvenile (n=21) MLD. Across cohorts, 28 children had gallbladder disease at baseline. After treatment, 14 (50%) had persistent gallbladder disease and another 5 children developed gallbladder disease after treatment.

The FDA label notes the following:

> 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 of age and an ARSA genotype consistent with LI MLD. Pre-symptomatic status* defined as the absence of neurological signs and symptoms of MLD.
> - 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.

*Pre-symptomatic children were permitted 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).

Efficacy outcomes were reported separately by cohort), as follows:

PSLI

The primary endpoint was severe motor impairment-free survival, defined as loss of locomotion ability and loss of sitting without support, or death. Data were available on 17 treated children until at least the age of 5 years. All of the treated children remained event-free, whereas all of the untreated children experienced events. Twelve of 17 treated children retained independent ambulation and another 2 children were able to ambulate without support at the time of last follow-up. In terms of cognitive function, at last follow-up, 19 of 20 treated children had cognitive performance scores above the threshold of severe cognitive impairment whereas there was a high level of severe cognitive impairment in the natural history cohort. For the outcome, overall survival, in children followed to at least 6 years of age, all 14 treated children were alive and 10 of 24 (42%) untreated children in the natural history cohort had died.

PSEJ

There were insufficient data on 3 children who were too young at last follow-up for efficacy evaluation, since symptom onset might not begin until 7 years of age in this form of MLD. Three of 7 children had evaluable motor outcomes. These 3 children retained normal gait, whereas, of the 2 matched sibling comparators, 1 developed impaired gait and 1 lost all motor function. Two of 7 treated children had evaluable cognitive outcomes and both retained stable normal cognitive function. One treated child died at age 2.1 years from a cerebral infarction.

ESEJ

Data wee available of 10 children with ESEJ, 2 of whom had a mild phenotype at baseline. During follow-up, 2 of 10 children (20%) died due to disease progression. Four children had favorable cognitive outcomes after treatment, with motor decline. The document states that motor and cognitive functioning typically decline together in untreated children with this form of MLD.

Data on 29 individuals considered by the FDA and discussed above were published by Fumagelli and colleagues in 2022. The authors reported on a phase I/II clinical trial evaluating atidarsagene autotemcel (NCT01560182). Outcomes in the 29 treated individuals were compared with a historical cohort of 31 individuals with early-onset MLD who participated in a non-interventional natural history study.

Eligibility for treatment included having a molecular and biochemical diagnosis of MLD of the PSLI, PSEJ or ESEJ form. Early-symptomatic was initially defined as presence of symptoms for less than 6 months and this definition was modified part-way through the study to be defined as individuals with an intelligence quotient (IQ) of 70 or greater and the ability to walk 10 or more steps independently; the change was made to prevent enrollment of more severely impaired individuals who were not expected to benefit from the therapy. Of the 29 treated individuals, 16 (55%) had late-infantile MLD and 13 (45%) had early-juvenile MLD.

According to clinicaltrials.gov (Orchard Therapeutics, 2023), the following were exclusion criteria of the Phase I/II trial:

- HIV RNA and/or HCV RNA and/or HBV DNA positive patients;
- Affected by neoplastic diseases;
- Cytogenetic alterations typical of MDS/AML;
- End-organ functions or any other severe disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study;
- Enrolled in other trials related to MLD treatment;
- Underwent allogeneic hematopoietic stem cell transplantation in the previous six months;
- Underwent allogenic hematopoietic stem cell transplantation with evidence of residual cells of donor origin.

The study's co-primary endpoints, assessed at 2 years after treatment, were:

- Improvement of more than 10% in the total score of the gross motor function measure (GMFM)-88 in treated patients compared with controls matched by age and disease subtype. The GMFM-88 total score can range from 0 to 264 (3 points per item) and a composite percentage score is calculated from the total score. A 10% difference between groups is considered a clinically relevant change.
- Change from baseline of total peripheral blood mononuclear cell (PBMC) ARSA activity.

For the first co-primary endpoint, at 2 years individuals with late-infantile MLD who were treated with atidarsagene autotemcel (n=11) had a GMFM-88 total score of 73.1% compared with a total score of 7.6% in untreated age-matched individuals with late-infantile MLD (n=5) in the natural history cohort. The treatment difference was 65.6% (95% confidence interval [CI], 48.9 to 82.3%), which exceeded the co-primary endpoint criterion of a 10% difference ($p<0.0001$).

For the second co-primary endpoint, mean ARSA activity in PBMCs, the lower limit of quantification (LLQ) was 25.79 nmol/mg/h. ARSA activity measured in PBMC at 2 years after treatment compared with pre-treatment values using a mixed-model repeated measures model.

Three deaths individuals occurred during the follow-up period, at 8 and 15 months after treatment, respectively. Two of the deaths were due to rapid disease progression in participants with early-juvenile MLD and were considered by investigators to be unrelated to treatment. The third death, in an individual with early juvenile MLD, was due to ischemic stroke following an infectious event 13.6 months after treatment. Data on this individual were limited e.g. there was no available post-mortem examination. However, on the basis of limited data, the investigators considered the death to be unrelated to the treatment.

All participants had at least one grade 3 or higher adverse event, the most commonly reported were febrile neutropenia (n=23, 79%), gait disturbance (n=15, 52%), and stomatitis (n=12, 41%). In addition, there were 3 (10%) individuals who had events of veno-occlusive disease, 2 (7%) who had events of thrombotic microangiopathy associated with conditioning, 2 (7%) who had metabolic acidosis (1 case of which was life-threatening and both of which resolved after treatment), 2 (7%) cases of gallbladder polyps requiring cholecystectomy, and 1 individual who required unmanipulated autologous back-up bone marrow. Most serious adverse events were considered to be related to conditioning or progression of the underlying MLD disease.

The analysis was based on a small number of individuals, particularly since the analysis was stratified by form of MLD. Moreover, individuals were not randomly assigned and the treatment group, but not the natural history comparison group, was subject to a number of inclusion and exclusion criteria increasing. Thus, it is likely that the treatment group were healthier at baseline than the

average individual with MLD and more likely to have better health outcomes over the following 2 years.

A Phase 3 clinical trial (NCT04283227) is underway. The two primary endpoints, which will both be assessed after 24 months of follow-up, are change from baseline in ARSA activity levels in cerebrospinal fluid (CSF) and change from baseline in neuronal metabolite ratio of N-acetyl-aspartate (NAA) to creatine (Cr) in white matter regions of interest of the brain.

Background/Overview

MLD is a rare genetic condition affecting approximately between 1 in 40,000 and 1 in 160,000 live births (National Organization for Rare Disorders [NORD], 2022). It primarily affects the nervous system, particularly the white matter of the brain and peripheral nerves. The condition is caused by mutations in the ARSA gene. Individuals with MLD do not produce sufficient amounts of the ARSA enzyme, and this deficiency leads to the accumulation of a fatty substance called sulfatide within cells. The buildup of sulfatide disrupts the formation and maintenance of the myelin sheath, which is essential for the proper conduction of nerve signals. MLD is progressive in nature and leads to severe neurological impairment.

Signs and Symptoms

Symptoms of MLD typically appear in early childhood, though there are different forms of the disease with varying ages of onset. Symptoms may include motor dysfunction, loss of cognitive ability, seizures, behavioral changes, and loss of vision and hearing. As the disease advances, affected individuals experience a gradual decline in their overall functioning, leading to severe disability. Peripheral neuropathy occurs with all forms of MLD and can be a presenting symptom, especially for individuals with the late-infantile form of MLD.

Diagnosis

MLD is typically diagnosed through a combination of clinical assessments, laboratory and imaging testing, and genetic testing (NORD, 2022; Shaimardanova, 2020).

Genetic testing involves looking for mutations in the ARSA and PSAP genes (in rare cases, people with MLD have mutations in the PSAP gene). There are hundreds of pathogenic ARSA variants associated with MLD. Two alleles A and I, account for a substantial proportion of MLD in certain populations. Individuals who are homozygous for the I allele tend to have very low or undetectable ARSA activity and late-infantile onset of MLD. Individuals who are homozygous for the A allele tend to have very low but still detectable ARSA activity and either juvenile- or adult-onset forms of MLD. Individuals with both I and A alleles tend to have juvenile onset MLD.

Biochemical diagnosis includes measurement of ARSA enzyme activity levels using samples from skin fibroblasts or leukocytes of individuals' blood and urine, and measurement of urinary sulfatide levels using mass spectrometry.

A diagnosis of MLD can be confirmed in individuals with progressive neurological dysfunction and/or leukodystrophy when there are all of the following:

- Biallelic ARSA pathogenic variants.
- Deficient levels of ARSA enzyme activity in leukocytes (typically ranging from less than 10 percent of normal to an undetectable level).
- Elevated levels of sulfatides in urine.

Other diagnostic tests include ultrasound to detect an increase in peripheral nerves. An increased size of peripheral nerves occurs with MLD; however, the test cannot be considered definitive because this increase also occurs with other metabolic disorders. Magnetic resonance imaging (MRI) of the brain can help confirm a diagnosis of MLD by showing the presence and absence of myelin; individuals with MLD have a distinctive pattern of myelin loss in the brain.

Forms of MLD include the following (NORD, 2022):

Late-Infantile MLD: This is the most common form of MLD; over half of children with MLD are diagnosed in the first 3 years of life when developmental delays and neurological symptoms become evident. The first sign is often having difficulty walking.

Juvenile MLD: This occurs in 20-30% of people with MLD and is defined by onset between 4 years old and adolescence (12-14 years old). Diagnosis for juvenile-onset MLD typically occurs when cognitive and motor deficits become noticeable.

Adult-Onset MLD: In a minority of cases, MLD may not be diagnosed until adulthood when symptoms such as psychiatric disturbances or subtle neurological changes appear.

MLD generally leads to premature death, typically within a few years to a couple of decades from symptom onset. Regardless of the form of the disease, the last stage is characterized by blindness, unresponsiveness, and an inability to move or speak. Individuals with the infantile form of MLD typically die by age 5 and those with juvenile MLD have progressive disease leading to death 10 to 20 years after onset. Individuals with the adult form of the disease typically live 6 to 14 years past the onset of symptoms (NINDS, 2023).

There is no cure for MLD at this time. Current treatments include symptom management, physical and occupational therapy, and psychological and emotional support. Stem cell transplantation can be considered in pre-symptomatic or minimally symptomatic children.

Allogeneic hematopoietic stem cell transplantation (HSCT) has been used as a treatment for MLD. A systematic review of studies on treatments for MLD (Armstrong, 2023) identified 8 studies (total n=172) that evaluated HSCT for individuals with MLD and reported survival outcomes. After approximately 5 years of follow-up, overall survival rates ranged from 57% to 74%. When examined by disease subtype, survival rates at 5 to 6 years after HSCT ranged from 50% to 60% in individuals with late-infantile MLD and from 59% to 82% in individuals with juvenile MLD.

Gene therapy is a new approach for treating MLD. The first gene therapy for MLD, atidarsagene autotemcel (Lenmeldy, Orchard Therapeutics), was approved by the FDA in March 2024. Atidarsagene autotemcel is an autologous hematopoietic stem- cell based gene therapy that involves extraction of CD34+ stem cells from the affected individual's bone marrow or blood. The stem cells are genetically modified *ex vivo* with a lentiviral vector encoding ARSA copy DNA (cDNA). Then, following myeloablative conditioning, the modified cells are infused into the individual intravenously. The aim of the treatment is for the corrected cells to proliferate and migrate to affected tissues where they will produce a functional version of the ARSA enzyme, which will then halt the progression of MLD.

According to the FDA: "LENMELDY 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) metachromatic leukodystrophy (MLD)".

The product is approved for single-dose administration. The following warnings and precautions were included in the product label:

• Thrombosis and Thromboembolic Events: Evaluate the risk factors for thrombosis prior to and after LENMEDLY infusion. Consider prophylaxis with anti-thrombotic agents prior to treatment with LENMELDY. (5.1)
• Encephalitis: Monitor children for signs or symptoms of encephalitis after treatment with LENMELDY. (5.2)
• Serious Infection: Monitor children for serious infection after myeloablative conditioning and LENMELDY infusion. (5.3)
• Veno-occlusive Disease: Monitor children for signs and symptoms of VOD including liver function tests in all patients during the first month after LENMELDY infusion. Consider prophylaxis for VOD. (5.4)
• Delayed Platelet Engraftment: Monitor children for thrombocytopenia and bleeding until platelet recovery is achieved. (5.5)
• Risk of Neutrophil Engraftment Failure: Monitor absolute neutrophil counts (ANC) after LENMELDY infusion. If neutrophil engraftment does not occur, administer rescue cells. (5.6)
• Risk of Insertional Oncogenesis: Monitor children for hematologic malignancies annually after treatment with LENMELDY. (5.7)
• Risk of Hypersensitivity Reactions: Monitor for hypersensitivity reactions during infusion. (5.8)

Definitions

Biallelic variant: Pertains to both alleles of a single gene (i.e., the paternal and maternal alleles).

Ex vivo: Outside of the body.

Lentiviral vector: A type of virus that is used as a vehicle for gene delivery. Lentiviral vectors are derived from Human immunodeficiency virus type-1 (HIV-1) lentivirus but are unable to replicate and hence are consider relatively safe.

Gene replacement therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction; also known as gene therapy.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

HCPCS	
C9399	Unclassified drugs or biologicals [when specified as Lenmeldy]
J3490	Unclassified drugs [when specified as Lenmeldy]
J3590	Unclassified biologics [when specified as Lenmeldy]

ICD-10 Diagnosis	
E75.25	Metachromatic leukodystrophy

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

References

Peer Reviewed Publications:

1. Armstrong N, Olaye A, Noake C, Pang F. A systematic review of clinical effectiveness and safety for historical and current treatment options for metachromatic leukodystrophy in children, including atidarsagene autotemcel. Orphanet J Rare Dis. 2023; 18(1):248.
2. 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.
3. Shaimardanova AA, Chulpanova DS, Solovyeva VV et al. Metachromatic leukodystrophy: Diagnosis, modeling, and treatment approaches. Front Med (Lausanne). 2020; 7:576221.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Food and Drug Administration (FDA). Lenmeldy™ package insert. Available at:https://www.fda.gov/media/177109/download. Accessed on March 21, 2024.
2. National Institute of Neurological Disorders and Stroke (NINDS). Metachromatic Leukodystrophy. January 2023. Available at: https://www.ninds.nih.gov/health-information/disorders/metachromatic-leukodystrophy. Accessed on March 13, 2024.
3. National Organization for Rare Disorders (NORD). Metachromatic Leukodystrophy. March 2022. Available at: https://rarediseases.org/rare-diseases/metachromatic-leukodystrophy/#affected. Accessed on March 13, 2024.
4. Orchard Therapeutics. Gene therapy for metachromatic leukodystrophy (MLD). NCT01560182; 2023. Available at: https://clinicaltrials.gov/study/NCT01560182?term=NCT01560182&rank=1. Accessed on March 13, 2024.
5. Orchard Therapeutics. OTL-200 in patients with late juvenile metachromatic leukodystrophy (MLD). NCT04283227: 2023. Available at: https://clinicaltrials.gov/study/NCT04283227?term=NCT04283227&rank=1. Accessed on March 13, 2024.

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Lenmeldy™

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	05/09/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.
Preliminary Discussion	02/15/2024	MPTAC Pre-FDA approval review.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

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. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.