Molina Clinical Policy
Lenmeldy (atidarsagene autotemcel) Policy No. 453

Last Approval: 4/10/2024
Next Review Due By: April 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Metachromatic leukodystrophy (MCLD) is an autosomal recessive, progressive, demyelinating disorder of the central and peripheral nervous system that, in its most severe form, leads to profound disability and shortened lifespan.

Mutations in the gene coding for the enzyme arylsulfatase A (ARSA) is the primary etiology of MCLD. ARSA metabolizes an important sulfatide lipid making up myelin called galactosylceramide-sulfate. Accumulation of lipid sulfatide secondary to poor metabolism, alters myelin membrane properties and leads to demyelination and neurodegeneration which in turn leads to loss of motor function and cognitive decline. Lipid sulfatide accumulation not only damages central and peripheral nerves but other tissues it builds up in, including kidneys, testes and gallbladder. MCLD is categorized as both a lysosomal storage disorder and a leukodystrophy (Saudubray 2012).

It is important to note that there is a more rare and different molecular etiology of MCLD resulting from another mutation in another gene called PSAP (Presaposin). It is important to confirm the presence of an ARSA mutation and not a PSAP mutation before considering gene therapy specifically aimed at adding back a functional copy of the ARSA gene. A functional copy of the ARSA gene will not correct MCLD due to PSAP mutations (Gomez-Ospina 2024).

It is also important to note the different clinical subtypes of ARSA-related MCLD because success of certain therapies differ based on the clinical subtype. There are three sub-types of ARSA-related MCLD differing in severity and symptom onset. Symptomatology in the late-onset infantile form occurs before 30 months of age and includes regression of language, cognition, and motor function (hypotonia, weakness, falls). This is followed by pain, spasticity, seizures and blindness. Demise often occurs on or before age 5 years.

Juvenile MCLD is subcategorized into early and late forms. Early-onset juvenile MCLD occurs between 30 months and 6 years where as late-onset juvenile MCLD occurs between 7-16 years of age. It often manifests in the educational setting, with noticeable declines in school performance, behavior issues and gait instability followed by progression similar to the infantile form.

In the adult-onset form of MCLD symptoms develop after 17 years of age although sometimes not until the forties. Declines in job performance, emotional instability and personality changes as well as psychosis occur. Weakness and incoordination leading to spasticity and seizures are typical. While the course of disease is progressive, prolonged periods of stability are possible. Despite periods of stability the path ultimately leads to a similar end stage seen in the infantile form.

Reported global incidences range from 1:40,000 to 1:170,000. MCLD is pan ethnic but certain populations have a higher prevalence (Habbanite Jewish, Israeli Arabs, Yup'ik from Alaska, and those of Navajo ancestry).

Diagnosis is based on typical symptomology, biochemical testing of sulfatide levels, ARSA enzyme activity and identification of bi-allelic mutations in the ARSA gene. Other helpful diagnostic assays are metachromatic lipid deposits on biopsy of nervous tissue and urine levels sulfatides (elevated).

There is no cure for MCLD. Therapies attempted include allogeneic bone marrow transplant, enzyme replacement and small molecule. Allogeneic bone marrow transplant is reported to delay onset and slow progression in pre-symptomatic patients, but severe impairment of gross motor function remains as does peripheral neuropathy. It also did not slow progression of disease in symptomatic individuals with early onset MCLD. Other therapies in early analyses have shown little efficacy and much of the focus in the early onset forms are focused on palliation.

In March 2024, a new gene / cell therapy was approved to treat MCLD due to bi-allelic mutations in the ARSA gene. Atidarsagene autotemcel (Lenmeldy, arsa-cel, OTL-200, Libmeldy in Europe) is a new, ex vivo gene therapy produced using CD34+ stem cells harvested from the patient. Those stem cells are transduced with a functional copy of the ARSA gene via lentiviral vector followed by cell expansion and then reinfusion back into the patient. The Phase 1 / 2 clinical trial leading to FDA approval (NCT01560182) was focused on presymptomatic late-onset infantile MCLD and early juvenile-onset MCLD patients (presymptomatic or early symptomatic). By definition, these two groups are all less than 7 years of age. Arsa-cel slowed demyelination, brain atrophy and led to preservation of cognitive function and motor development in most patients (Fumagalli 2022). Patients with severe impairments or in the rapid phase of disease progression may not benefit from treatment.

The phase III clinical trial (NCT04283227) is ongoing and scheduled to conclude in March 2025. It focuses on late-onset juvenile MCLD.

RELATED POLICIES

MCP-184: Experimental and Investigational Services

COVERAGE POLICY

Atidarsagene autotemcel **may be considered medically necessary** when the following criteria are met:

1. Diagnosis of metachromatic leukodystrophy (MCLD) based on
    a. Genetic testing confirming bi-allelic mutations in the ASRA gene.
        i. 0/R or R/R genotype or a genotype recognized as associated with either late-onset infant MCLD or early-onset juvenile MCLD.
        ii. 0 genotype (null allele) produces no detectable, functional arylsulfatase A enzyme activity.
        iii. R genotype (R for residual) produces residual activity of arylsulfatase A activity (< 1% activity when assayed with physiologic substrates)
        iv. If novel ARSA gene mutations are suspected, in-silico predictions along with 24-hour urine collections of sulfatide levels must be elevated.
    b. Biochemical testing indicates ARSA activity below normal ranges in peripheral blood mononuclear cells or fibroblasts.
    c. Urinary sulfatide levels in 24-hour collection are elevated beyond what would be possible for MCLD carriers or ARSA pseudo-deficiency.
2. Member is clinically diagnosed as presymptomatic, late-onset infantile form or early-onset juvenile form or symptomatic early-onset juvenile MCLD.
    a. If member is symptomatic and their age at symptom-onset falls within the early-onset juvenile MCLD timeframe (> 30 months and < 7 years of age), the member's symptom is mild, isolated, and stable (symptom has not progressed). The member can walk independently (Gross Motor Function Classification – Metachromatic LeukoDystrophy (GMFC-MLD) Level 0 with ataxia or GMFC-MLD Level 1). *Note: symptom onset during infantile form is often followed by rapid decline. Treatment within the period of rapid decline / progression has been ineffective and busulfan conditioning may be especially harmful. Treatment of late-onset juvenile form is under study.*
    b. Signs of disease on instrumental evaluations (electroneurography and brain MRI) or abnormal reflexes

or clonus are allowed.

c. If the member is diagnosed with either presymptomatic late-onset infantile MCLD or early-onset juvenile MCLD, both of which occur at < 7 years of age, normal exams are required (normal motor milestones achieved, normal gross motor function according to chronological age and normal neurological examination (if applicable based on the age of the subject, GMFC-MLD = 0)). Abnormal reflexes or clonus are allowed.

d. If a member is pre-symptomatic, genotype-phenotype predictions or the age of onset of an affected family member can be used to estimate MCLD form.

3. The member has a cognitive function as defined by an IQ ≥ 85 on age-appropriate cognitive scales.
4. Documentation of negative HIV testing (negative HIV RNA and/or anti-p24 antibodies).
5. Member does not have malignant neoplasia (except localized skin cancer) or a documented history of hereditary cancer syndrome. Prior successfully treated malignancy without evidence of recurrence (based on oncologist opinion) are allowed.
6. No history of myelodysplasia, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) or other serious hematological disorders.
7. Member is not eligible or currently enrolled in other interventional trials.
8. Member has not previously undergone allogeneic hematopoietic stem cell-gene therapy or had prior gene therapy.
9. No history of active, symptomatic herpes zoster.
10. No evidence of active tuberculosis (TB) based on medical examination, chest imaging and TB testing.
11. No evidence of acute or chronic hepatitis B (HBV) as evidenced by positive Hepatitis B surface antigen (HBsAg) test result within 3 months prior to onset of conditioning and/or positive HBV DNA.
    a. Members with positive hepatitis B core antibody due to prior resolved disease must have a confirmatory negative HBsAg and negative Hepatitis B DNA test.
12. Negative Hepatitis C RNA testing. NOTE: Patients previously testing positive for antibodies to hepatitis C can be treated, provided they demonstrate absence of ongoing infection using a nucleic acid test with a limit of quantification of ≤15 international units/ml. Negative test results are required on at least 3 sequential occasions over a period of at least 4 weeks, after completion of hepatitis C treatment, with the final test conducted no more than 3 days prior to cell harvest.
13. No evidence of end-organ dysfunction, severe active infection unresponsive to treatment, or other severe disease or clinical condition.
14. A negative pregnancy test is required in females of childbearing potential.
15. Males capable of fathering a child and females of childbearing age should use an effective method of contraception from start of mobilization through at least 6 months after administration of LENMELDY.

Limitations and Exclusions

The safety and efficacy of LENMELDY therapy is not established in children with the late-onset juvenile form of MCLD. Lenmeldy has not been studied in children with renal or hepatic impairment. LENMELDY must not be administered during pregnancy because of the risk associated with myeloablative conditioning.

QUANTITY LIMITATIONS: FDA approved dosing with one-time dose per lifetime. Additional infusions of arsa-cel will not be authorized.

CONTINUATION OF THERAPY

Lenmeldy (atidarsagene autotemcel) is indicated as a one-time infusion only. Repeat treatment or re-administration of a dose is not supported by labeling or compendia and is not considered medically necessary.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Phase 1 / 2 study (NCT01560182) was a prospective, non-randomized trial that began in 2010 and later expanded access to twenty-nine patients: 16 with late-onset infantile MCLD and 13 with early-onset juvenile MCLD. After cell harvest, busulfan pre-conditioning was required. The comparator was a cohort of thirty-one patients with early onset MCLD from a non-interventional natural history study from 2000-2017. Median follow-up was 3.16 years for treated patients.

The primary endpoint for this phase 1 /2 trial was the demonstration of 10% improvement in gross motor function as compared to natural history controls at 2 years post arsa-cel infusion. The authors felt this level of improvement would establish clinically meaningful efficacy of arsa-cel. Results exceeded this threshold. Mean differences in gross motor function between treated groups and controls were significant for late infantile (66%; CI 48.9 – 82.3) and early juvenile (42%; CI 12.3-71.8) MCLD patients. Performance and verbal IQ scores remained within normal range for most treated patients. Nerve conduction studies looking at peripheral effects of the arsa-cel treatment group also showed improvement in late-onset, infant MCLD.

The co-primary endpoint for the Phase 1 / 2 study was a meaningful improvement in PBMC ARSA activity as compared to controls. All patients showed reconstituted ASRA activity in PBMCs at 3 months, ASRA activity in CSF (undetectable at baseline) was supra normal at 3 months and normalized and stabilized by 6-12 months post treatment.

In addition to natural history controls used for the statistical analyses, comparison with available untreated siblings confirmed the main treatment effects.

Two patients with cognitive impairment at baseline had disease progression between enrollment and treatment and had motor and cognitive deterioration similar to controls post treatment. One other patient borderline for symptomatic expression of disease had progression albeit delayed relative to controls.

26 of 29 participants were alive at the time of the data cut. All patients had a minimum of 3 years follow-up and some as long as 7.5 years. Two deaths occurred secondary to rapid progression of disease unrelated to arsa-cel therapy. One presymptomatic early juvenile MCLD patient expired due to ischemic stroke post infection 13.6 months after treatment. Prior to this event the patient had normal neurologic examination, neuroimaging motor and cognitive development at the 12-month mark post arsa-cel infusion. This death was thought to be unrelated to arsa-cel but it cannot be ruled out. All patient achieved hematologic engraftment.

Grade 3 or higher adverse events attributed to busulfan conditioning included febrile neutropenia, thrombotic microangiopathy, veno-occlusive disease, stomatitis. Four patients experienced treatment related events secondary to anti-arsa antibodies that resolved spontaneously or with rituximab treatment. There was no evidence of malignant clonal expansion or oncogenic transformation. Other adverse events such as gait disturbance were attributed to disease progression.

Additional data across multiple trials were made available to the FDA for accelerated approval and are noted in the prescribing information but are not published in aggregate form yet. The additional data reported in the FDA label are confirmatory of the positive results reported in the phase 1/2 trial. This additional data was presented at a recent conference but is not yet available in a peer reviewed journal (Fumagalli 2023). When the additional results are published this policy will be updated.

A phase III clinical trial (NCT04283227) is ongoing and scheduled to conclude in March 2025. It focuses on late-onset

juvenile MCLD.

National/Specialty Organizations

The Institute for Clinical and Economic Review (ICER) assessed the efficacy and value of atidarsagene autotemcel ("arsa-cel") for metachromatic leukodystrophy (MCLD). The panel concluded the evidence for net health benefit was favorable and if arsa-cel pricing was consistent with the current European price, it would be cost-effective for late-onset infantile, early-onset presymptomatic or early-onset symptomatic MCLD.

In 2022, the United Kingdom's National Institute for Health and Care Excellence (NICE) published guidance for atidarsagene autotemcel for treating MCLD (arsa-cel already approved in Europe). NICE recommends arsa-cel for children with early-onset juvenile MCLD who can still walk independently and have no cognitive deficit and for children with late infantile or early-onset juvenile forms without signs or symptoms.

SUPPLEMENTAL INFORMATION

Seven levels of gross motor function classification in metachromatic leukodystrophy (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	(a) Sitting without support but no locomotion **or** (b) 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

(Kehrer 2011)

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

Code	Description
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 (Healthcare Common Procedure Coding System) Code

Code	Description
C9399	Unclassified drugs or biologicals [when specified as Lenmeldy (Atidarsagene autotemcel)

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

4/10/2024 New policy. IRO Peer Review on March 24, 2024, by a practicing physician board-certified in Neurology.

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