MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

Gene Therapies for Cerebral Adrenoleukodystrophy

Table of Contents

Policy Number: 241

BCBSA Reference Number: 5.01.45 (For Plan internal use only)

Related Policies

Gene Therapy for Cerebral Adrenoleukodystrophy Skysona® (Elivaldogene autotemcel) Prior Authorization Request Form #242

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Elivaldogene autotemcel is considered **MEDICALLY NECESSARY** for individuals if they meet criteria 1 through 5:

1. Individual is 4 to 17 years of age at the time of infusion of elivaldogene autotemcel.
2. Documented diagnosis of active cerebral X-linked adrenoleukodystrophy as defined by:
    a. Confirmed mutation in the *ABCD1* gene; **AND**
    b. Elevated very-long-chain fatty acids (VLCFAs); **AND**
    c. Presence of active central nervous system (CNS) disease documented by:
        i. Loes score between 0.5 and 9 (inclusive) on the 34-point scale,]; **AND**
        ii. Gadolinium enhancement on MRI of demyelinating lesions.
3. Documented neurologic function score (NFS) score ≤1.
4. Individual **DOES NOT** have **ANY** of the following:
    a. History of receiving prior gene therapy or allogeneic hematopoietic stem cell transplant.
    b. Hematological compromise as evidenced by **ANY** of the following:
        i. Peripheral blood absolute neutrophil count (ANC) count <1500 cells/mm^3;
        ii. Platelet count <100,000 cells/mm^3 **OR** hemoglobin <10 g/Dl;
        iii. Uncorrected bleeding disorder.
    c. Hepatic compromise as evidenced by **ANY** of the following:
        i. Aspartate transaminase (AST) >2.5 × upper limit of normal (ULN); **OR**
        ii. Alanine transaminase (ALT) >2.5 × ULN; **OR**
        iii. Total bilirubin value >3.0 mg/dL, except if there is a diagnosis of Gilbert's Syndrome and the participant is otherwise stable.
    d. Cardiac compromise as evidenced by left ventricular ejection fraction <40%.
    e. Baseline estimated glomerular filtration rate <70 mL/min/1.73 m^2 or actual or calculated creatinine clearance <50 mL/min.

f. Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (Including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome and family adenomatous polyposis).
g. Any clinically significant uncontrolled, active bacterial, viral, fungal, parasitic, or prion associated infection, including but not limited to positive human immunodeficiency virus (HIV-1 or HIV-2), human T lymphotropic virus 1 (HTLV-1), active hepatitis B virus, and hepatitis C virus.
h. Any condition(s) that are contraindicated for continued MRI studies.
i. Absence of adequate contraception for fertile patients.
j. Any contraindications to the use of granulocyte colony-stimulating factor (G-CSF) or plerixafor during the mobilization of hematopoietic stem cells, and any contraindications to use the use of busulfan or fludarabine, including known hypersensitivity to the active substances or to any of the excipients in their formulations.

Elivaldogene autotemcel is considered **INVESTIGATIONAL** when the above criteria are not met.

Elivaldogene autotemcel is considered **INVESTIGATIONAL** for all other indications.

Repeat treatment of elivaldogene autotemcel is considered **INVESTIGATIONAL**.

Policy Guidelines

Recommended Dose

The minimum recommended dose is 5.0×10^6 CD34+ cells/kg of body weight.

Dosing Limits

One injection per lifetime.

Other Considerations

- Elivaldogene autotemcel was not studied in combination with statins, Lorenzo's Oil, or dietary regimens used to lower VLFCA levels.
- Prescriber's discretion is advised regarding the continuation of VLFCA lowering treatments after elivaldogene autotemcel administration.
- Where feasible, the individual's vaccination should be up to date with all age-appropriate vaccinations before elivaldogene autotemcel administration.
- Where feasible, the individual should receive periodic monitoring for hematological malignancies, including Myelodysplastic Syndrome (MDS).
- Final administration of elivaldogene autotemcel may be limited based on the myeloablative and lymphodepleting conditioning requirements.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required**.
Commercial PPO and Indemnity	Prior authorization is **required**.
Medicare HMO Blue℠	Prior authorization is **required**.
Medicare PPO Blue℠	Prior authorization is **required**.

Requesting Prior Authorization Using Authorization Manager

Providers will need to use Authorization Manager to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request

authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the request is processed accurately and quickly:
- Enter the facility's NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

Authorization Manager Resources
Refer to our Authorization Manager page for tips, guides, and video demonstrations.

Complete Prior Authorization Request Form for Cerebral Adrenoleukodystrophy Skysona® (Elivaldogene autotemcel) (242) using Authorization Manager.

For out of network providers: Requests should still be faxed to 888-973-0726.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
XW043F3	Introduction of Other New Technology Therapeutic Substance into Central Vein, Percutaneous Approach, New Technology Group 3 (no specific code for this drug)
XW043F5	Introduction of Other New Technology Therapeutic Substance into Central Vein, Percutaneous Approach, New Technology Group 5

Description

Cerebral adrenoleukodystrophy (CALD) is an X-linked genetic neurodegenerative disease that most severely affects individuals assigned male at birth. The genetic mutation leads to impaired or loss of adrenoleukodystrophy protein (ALDP) expression.

X-linked adrenoleukodystrophy is established in a male (assigned male at birth or AMAB) with suggestive clinical findings and elevated very long chain fatty acids (VLCFA), with the majority having inherited a pathogenic variant in the *ABCD1* gene. While female (assigned female at birth or AFAB) carriers can develop spastic paraparesis most often in adulthood, adrenal function is generally not impaired. CALD

typically only affects AMAB in childhood and AFAB with CALD are very rare. Defective function of ALDP leads to the accumulation of very long-chain fatty acids (VLCFAs), which occurs in plasma and all tissue types but most prominently in the adrenal cortex and white matter of the brain and spinal cord. VLCFAs initiate an inflammatory cascade ultimately leading to inflammatory cerebral demyelination. In general, once clinical symptoms appear, the clinical course is rapid with progressive cognitive and neurologic deficits leading to major disability including cortical blindness, incontinence, requirement for tube feeding, loss of communication, loss of ambulation, loss of voluntary movement, and ultimately premature death. Prior to the approval of elivaldogene autotemcel, there were no approved treatments for CALD in the US. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered the standard of care and has been shown to stabilize neurologic function, with better outcomes observed in patients treated at the early stages of cerebral involvement and among those who receive human leukocyte antigen (HLA)-matched transplant versus HLA-mismatched transplant. Challenges associated with HSCT include serious immunologic complications, including transplant-related mortality, graft rejection, and graft-versus-host disease. Elivaldogene autotemcel is an autologous hematopoietic stem cell (HSC)-based gene therapy which adds functional copies of the *ABCD1* cDNA into patients' HSCs through transduction of autologous CD34+ cells with Lenti-D lentiviral vector. After infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes (CD14+) capable of producing functional ALDP. Functional ALDP can then participate in the local degradation of VLCFAs, which is believed to slow or possibly prevent further inflammation and demyelination.

Summary

For individuals who are assigned male at birth and 4 to 17 years of age with early, active cerebral adrenoleukodystrophy (CALD) who receive elivaldogene autotemcel, the evidence includes a single post-hoc analysis from 2 single-arm interventional studies and 2 non-concurrent historical control studies. The interventional studies enrolled patients with early, active CALD as defined by Loes score between 0.5 and 9 (inclusive) and gadolinium enhancement on magnetic resonance imaging (MRI), as well as a neurologic function score (NFS) of ≤1, indicating limited changes in neurologic function. The *post-hoc* analysis in an enriched sample of symptomatic study participants compared time from onset of symptoms (NFS ≥1) to time to first major functional disability (MFD) or death (i.e., MFD-free survival) in treated (n=11) and natural history untreated (n=7) individuals. Relevant outcomes of interest are overall survival, disease-specific survival, change in disease status, functional outcomes, quality of life, treatment-related morbidity and treatment-related mortality. The estimated MFD-free survival at month 24 from time of first NFS ≥1 were 72% (95% CI, 35%-90%) for the symptomatic elivaldogene autotemcel treated subpopulation and 43% (95% CI, 10%-73%) for the natural history subpopulation. Notable limitations include post-hoc analysis using a historical control with a limited sample size and known differences in the baseline prognostic variables such as age at enrollment, age at first NFS ≥1, Loes score, and distribution of brain MRI pattern of disease between the 2 groups. As a result, it is difficult to determine whether the observed effect was due to a treatment effect or due to treatment at an early stage of disease with insufficient duration of follow-up to detect progression to MFD or death. In addition to the significant uncertainty about efficacy, 3 cases of myelodysplastic syndrome mediated by Lenti-D lentiviral vector integration into proto-oncogenes were reported. Given that 1 of the 3 cases of hematological malignancy occurred 7.5 years after administration of gene therapy, long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
1/2024	Clarified coverage and updated IC to align with 118E MGL § 51A.
7/2023	Reformatted Policy.
02/2023	New medical policy describing medically necessary indications. Policy created with literature review through October 24, 2022. The use of elivaldogene autotemcel is considered medically appropriate for individuals with childhood cerebral X-linked adrenoleukodystrophy when certain conditions are met. Effective 02/01/2023.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. Brain. Aug 1997; 120 (Pt 8): 1485-508. PMID 9278636
2. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. Nat Clin Pract Neurol. Mar 2007; 3(3): 140-51. PMID 17342190
3. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. AJNR Am J Neuroradiol. Oct 1994; 15(9): 1761-6. PMID 7847225
4. Moser HW, Loes DJ, Melhem ER, et al. X-Linked adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. Neuropediatrics. Oct 2000; 31(5): 227-39. PMID 11204280
5. Moser HW, Raymond GV, Dubey P. Adrenoleukodystrophy: new approaches to a neurodegenerative disease. JAMA. Dec 28 2005; 294(24): 3131-4. PMID 16380594
6. Mallack EJ, Turk BR, Yan H, et al. MRI surveillance of boys with X-linked adrenoleukodystrophy identified by newborn screening: Meta-analysis and consensus guidelines. J Inherit Metab Dis. May 2021; 44(3): 728-739. PMID 33373467
7. Loes DJ, Fatemi A, Melhem ER, et al. Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. Neurology. Aug 12 2003; 61(3): 369-74. PMID 12913200
8. Melhem ER, Loes DJ, Georgiades CS, et al. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging in predicting disease progression. AJNR Am J Neuroradiol. May 2000; 21(5): 839-44. PMID 10815658
9. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. Blood. Aug 01 2004; 104(3): 881-8. PMID 15073029
10. Shapiro E, Krivit W, Lockman L, et al. Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. Lancet. Aug 26 2000; 356(9231): 713-8. PMID 11085690
11. Mosser J, Douar AM, Sarde CO, et al. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. Nature. Feb 25 1993; 361(6414): 726-30. PMID 8441467
12. Executive Summary: X-linked adrenoleukodystrophy (X-ALD) to the Recommended Uniform Screening Panel. Available at https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/x-ald-exsum.pdf. Last accessed Nov 8, 2022
13. Hubbard WC, Moser AB, Liu AC, et al. Newborn screening for X-linked adrenoleukodystrophy (X-ALD): validation of a combined liquid chromatography-tandem mass spectrometric (LC-MS/MS) method. Mol Genet Metab. Jul 2009; 97(3): 212-20. PMID 19423374
14. Raymond GV, Jones RO, Moser AB. Newborn screening for adrenoleukodystrophy: implications for therapy. Mol Diagn Ther. 2007; 11(6): 381-4. PMID 18078355
15. Kemper AR, Brosco J, Comeau AM, et al. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. Genet Med. Jan 2017; 19(1): 121-126. PMID 27337030
16. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. Blood. Aug 18 2011; 118(7): 1971-8. PMID 21586746
17. Aubourg P, Blanche S, Jambaqué I, et al. Reversal of early neurologic and neuroradiologic manifestations of X-linked adrenoleukodystrophy by bone marrow transplantation. N Engl J Med. Jun 28 1990; 322(26): 1860-6. PMID 2348839
18. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. Aug 13 2012; 7: 51. PMID 22889154

19. Raymond GV, Aubourg P, Paker A, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. Mar 2019; 25(3): 538-548. PMID 30292747
20. Summary Basis for Regulatory Action for Elivaldogene Autotemcel. Available at https://www.fda.gov/media/162098/download. Accessed October 31, 2022
21. Mahmood A, Dubey P, Moser HW, et al. X-linked adrenoleukodystrophy: therapeutic approaches to distinct phenotypes. Pediatr Transplant. Dec 2005; 9 Suppl 7: 55-62. PMID 16305618
22. Kühl JS, Kupper J, Baqué H, et al. Potential Risks to Stable Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Children With Cerebral X-linked Adrenoleukodystrophy. JAMA Netw Open. Jul 06 2018; 1(3): e180769. PMID 30646031
23. Prescribing Label: Skysona (elivaldogene autotemcel) suspension for intravenous infusion. Initial U.S. Approval: 2022. Available at https://https://www.fda.gov/media/161640/download
24. Chiesa R, Boelens JJ, Duncan CN, et al. Variables affecting outcomes after allogeneic hematopoietic stem cell transplant for cerebral adrenoleukodystrophy. Blood Adv. Mar 08 2022; 6(5): 1512-1524. PMID 34781360
25. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. N Engl J Med. Oct 26 2017; 377(17): 1630-1638. PMID 28976817
26. Engelen M, van Ballegoij WJC, Mallack EJ, et al. International Recommendations for the Diagnosis and Management of Patients with Adrenoleukodystrophy: A Consensus-Based Approach. Neurology. Nov 22 2022; 99(21): 940-951. PMID 36175155