



MASSACHUSETTS

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Medical Policy Gene Therapies for Cerebral Adrenoleukodystrophy

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Policy Number: 241

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

Related Policies

None

Prior Authorization Information

<input checked="" type="checkbox"/> Prior Authorization <input type="checkbox"/> Step Therapy <input type="checkbox"/> Quality Care Dosing		Pharmacy Operations: Tel: 1-800-366-7778 Fax: 1-800-583-6289
		Policy last updated 1/2024
Pharmacy (Rx) or Medical (MED) benefit coverage	<input type="checkbox"/> Rx <input checked="" type="checkbox"/> MED	To request for coverage: Physicians may call, fax, or mail the attached form (Formulary Exception/Prior Authorization form) to the address below.
Policy applies to Commercial Members: <ul style="list-style-type: none"> • Managed Care (HMO and POS), • PPO and Indemnity • MEDEX with Rx plan • Managed Major Medical with Custom BCBSMA Formulary • Comprehensive Managed Major Medical with Custom BCBSMA Formulary • Managed Blue for Seniors with Custom BCBSMA Formulary 		Blue Cross Blue Shield of Massachusetts Pharmacy Operations Department 25 Technology Place Hingham, MA 02043 Individual Consideration: Policy for requests that do not meet clinical criteria of this policy, see section labeled Individual Consideration

Policy

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

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

This form **must** be completed and faxed to: **Medical and Surgical: 1-888-282-0780; Medicare Advantage: 1-800-447-2994.**

Click here for [Gene Therapy for Cerebral Adrenoleukodystrophy Skysona® \(Elivaldogene autotemcel\) Prior Authorization Request Form, #242](#)

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/mm³;
 - ii. Platelet count $< 100,000$ cells/mm³ **OR** hemoglobin < 10 g/Dl;
 - iii. Uncorrected bleeding disorder.
 - c. Hepatic compromise as evidenced by **ANY** of the following:
 - i. Aspartate transaminase (AST) $> 2.5 \times$ upper limit of normal (ULN); **OR**
 - ii. Alanine transaminase (ALT) $> 2.5 \times$ 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 m² 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 VLFCFA levels.
- Prescriber's discretion is advised regarding the continuation of VLFCFA 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.

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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.

Individual Consideration

Our medical policies are written for most people with a given condition. Each policy is based on peer reviewed clinical evidence. We also take into consideration the needs of atypical patient populations and diagnoses.

If the coverage criteria outlined is unlikely to be clinically effective for the prescribed purpose, the health care provider may request an exception to cover the requested medication based on an individual's unique clinical circumstances. This is also referred to as "individual consideration" or an "exception request."

Some reasons why you may need us to make an exception include: therapeutic contraindications; history of adverse effects; expected to be ineffective or likely to cause harm (physical, mental, or adverse reaction).

To facilitate a thorough and prompt review of an exception request, we encourage the provider to include additional supporting clinical documentation with their request. This may include:

- Clinical notes or supporting clinical statements.
- The name and strength of formulary alternatives tried and failed (if alternatives were tried) and specifics regarding the treatment failure, if applicable.
- Clinical literature from reputable peer reviewed journals.
- References from nationally recognized and approved drug compendia such as American Hospital Formulary Service[®] Drug Information (AHFS-DI), Lexi-Drug, Clinical Pharmacology, Micromedex or Drugdex[®]; and
- References from consensus documents and/or nationally sanctioned guidelines.

Providers may call, fax or mail relevant clinical information, including clinical references for individual patient consideration, to:

Blue Cross Blue Shield of Massachusetts
 Pharmacy Operations Department
 25 Technology Place
 Hingham, MA 02043
 Phone: 1-800-366-7778
 Fax: 1-800-583-6289

We may also use prescription claims records to establish prior use of formulary alternatives or to show if step therapy criteria has been met. We will require the provider to share additional information when prescription claims data is either not available or the medication fill history fails to establish use of preferred formulary medications or that step therapy criteria has been met.

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](#)

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