Clinical Policy: Elivaldogene Autotemcel (Skysona)

Reference Number: CP.PHAR.556
Effective Date: 09.16.22
Last Review Date: 11.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Elivaldogene autotemcel (Skysona®) is a genetically modified autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced ex vivo with a lentiviral vector encoding *ABCD1* complementary deoxyribonucleic acid (cDNA) for human adrenoleukodystrophy protein.

FDA Approved Indication(s)

Skysona is indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD) without an available human leukocyte antigen (HLA)-matched donor for allogeneic hematopoietic stem cell transplant. Early, active CALD refers to asymptomatic or mildly symptomatic (neurologic function score, NFS ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5-9.

This indication is approved under accelerated approval based on 24-month Major Functional Disability (MFD)-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitation(s) of use:

- Skysona does not treat or prevent adrenal insufficiency due to adrenoleukodystrophy.
- An immune response to Skysona may limit the persistence of descendent cells of Skysona, causing rapid loss of efficacy of Skysona in patients with full deletions of the human adenosine triphosphate binding cassette, sub family D, member (*ABCD1)* gene.
- Skysona has not been studied in CALD secondary to head trauma.
- Given the risk of hematologic malignancy with Skysona, and unclear long-term durability of Skysona and human adrenoleukodystrophy protein (ALDP) expression, careful consideration should be given to the timing of treatment for each boy and treatment of boys with isolated pyramidal tract disease since their clinical symptoms do not usually occur until adulthood.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

All requests reviewed under this policy **require medical director review.**

It is the policy of health plans affiliated with Centene Corporation® that Skysona is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

**Only for initial treatment dose; subsequent doses will not be covered.*

A. Cerebral Adrenoleukodystrophy (must meet all)**:**

1. Diagnosis of adrenoleukodystrophy with both of the following (a and b):
   a. Genetic confirmation of *ABCD1* mutation;
   b. Elevated levels of very long chain fatty acids (VLCFA);
2. Prescribed by or in consultation with both of the following (a and b):
   a. Neurologist;
   b. Transplant specialist;
3. Member is a biologic male;
4. Age between 4 and 17 years;
5. Early, active CNS disease established by brain MRI demonstrating both of the following (a and b):
   a. Loes score ≥ 0.5 and ≤ 9 on the 34-point scale (*see Appendix D*);
   b. Gadolinium enhancement of demyelinating lesions on MRI;
6. Member has an NFS ≤ 1 (*see Appendix D*);
7. Member has no available HLA-matched (i.e., full HLA-matching of all evaluated alleles) donor;
8. Transplant specialist attestation that member is clinically stable and eligible to undergo myeloablative conditioning and HSCT;
9. Member has not received prior allogeneic HSCT;
10. Member has not received prior gene therapy;
11. For members with CALD and isolated pyramidal tract disease: Hematology specialist attestation of both of the following (a and b):
    a. Member understands the potential increased risk of malignancy associated with Skysona treatment;
    b. Applicable hematology assessments have been performed (*see Appendix E for examples*);
12. Member is not positive for the presence of HIV type 1 or 2;
13. Dose contains a minimum of 5×10^6 CD34+ cells/kg.

Approval duration: 3 months (one time infusion per lifetime)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Cerebral Adrenoleukodystrophy

1. Continued therapy will not be authorized as Skysona is indicated to be dosed one time only.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 2 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ABCD1: adenosine triphosphate binding cassette, sub family D, member 1
ALDP: adrenoleukodystrophy protein
CALD: cerebral adrenoleukodystrophy
cDNA: complementary deoxyribonucleic acid
FDA: Food and Drug Administration
HLA: human leukocyte antigen
HSCT: hematopoietic stem cell transplantation
MFD: major functional disability
MRI: magnetic resonance imaging
NFS: neurologic function score
VLCFA: very long chain fatty acids

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): none
- Boxed warning(s): hematologic malignancy

Appendix D: General Information
- The Loes score is a rating of the severity of abnormalities in the brain found on MRI. It ranges from 0 to 34, based on a point system derived from the location and extent of disease and the presence of atrophy in the brain, either localized to specific points or generally throughout the brain. A score of 0 indicates a normal MRI, and higher scores indicate increased severity of cerebral lesions.
- The CALD NFS is a 25-point score used to evaluate the severity of gross neurologic dysfunction across 15 symptoms in six categories. An NFS of 0 indicates that there is no observed impairment in the neurologic functions that are assessed on the 25-point scale, and higher scores correspond to increasing severity of functional deficits.
- Hematologic malignancies, including life-threatening cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), have developed in patients treated with Skysona in clinical studies between 14 months and 10 years after Skysona administration, and the cancers appear to be related to treatment with Skysona. Death related to treatment for malignancy and relapse of malignancy have occurred.

Appendix E: Baseline Hematologic Assessments for CALD with isolated pyramidal tract disease
- Complete blood count with differential
- Hematopathology review of peripheral blood smear
- Hematopathology review of bone marrow biopsy (core and aspirate) with flow cytometry, conventional karyotyping, and next generation sequencing (NGS) with a molecular panel appropriate for age and including coverage for gene mutations expected in myeloid and lymphoid malignancies
- Testing for germline mutations that are associated with hematologic malignancy

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CALD	Minimum recommended dose: 5.0×10^6 CD34+ cells/kg	None

VI. Product Availability
Single-dose cell suspension: up to two infusion bags of genetically modified autologous cells enriched for CD34+ cells labeled for the specific recipient

VII. References
1. Skysona Prescribing Information. Somerville, MA: bluebird bio, Inc.; August 2025. Available at: https://www.bluebirdbio.com/-/media/bluebirdbio/Corporate%20COM/Files/SKYSONA/SKYSONA_prescribing_information.pdf. Accessed August 8, 2025.

2. ClinicalTrials.gov. A phase 2/3 study of the efficacy and safety of hematopoietic stem cells transduced with Lenti-D lentiviral vector for the treatment of cerebral adrenoleukodystrophy (CALD). Available at: https://clinicaltrials.gov/ct2/show/NCT01896102. Accessed August 8, 2025.
3. ClinicalTrials.gov. A clinical study to assess the efficacy and safety of gene therapy for the treatment of cerebral adrenoleukodystrophy (CALD). Available at https://clinicaltrials.gov/ct2/show/NCT03852498. Accessed August 7, 2024.
4. 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. 2022;99(21):940-951.
5. 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 Journal of Rare Diseases 2012;7:51.
6. Zhu J, Eichler F, Biffi A, et al. The changing face of adrenoleukodystrophy. Endocr Rev. 2020 August;41(4):577-593.
7. ALD Info. Diagnosis of ALD. Available at: https://adrenoleukodystrophy.info/clinical-diagnosis/diagnosis-of-ald. Accessed August 7, 2025.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3590	Unclassified biologics
C9399	Unclassified drugs or biologicals

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	08.17.21	11.21
4Q 2022 annual review: drug is now FDA approved – criteria updated per FDA labeling: removed endocrinologist option; added transplant specialist requirement; clarified male member is a biologic male; clarified that age is between 4 and 17 years old; added criterion that that the member does not have an available HLA-matched donor and understands the risks and benefits of alternative therapeutic options such as allogeneic HSCT; added criterion for attestation from transplant specialist that member is clinically stable; added criterion for hematology specialist attestation for CALD with isolated pyramidal tract disease that member understands malignancy risk and has had applicable hematology assessments listed in Appendix F; added exclusion for HIV-1 and HIV-2; updated dosing criterion to a minimum dose per	10.11.22	11.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
FDA labeling; clarified that Skysona is indicated to be dosed one time only in Section II; references reviewed and updated.		
4Q 2023 annual review: no significant changes; references reviewed and updated.	07.10.23	11.23
4Q 2024 annual review: no significant changes; removed Appendix E VLCFA lab reference ranges; added hematologic malignancy information to Appendix D; references reviewed and updated.	07.19.24	11.24
4Q 2025 annual review: RT4: updated FDA-approved indication to include lack of an available HLA-matched donor for allogeneic HSCT; removed criterion option for having an HLA-matched donor and its accompanying criteria per PI; references reviewed and updated.	08.08.25	11.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.