Clinical Policy: Elivaldogene Autotemcel (Skysona)

Reference Number: ERX.SPA.452
Effective Date: 09.16.22
Last Review Date: 11.22
Line of Business: Commercial, Medicaid

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). 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.
- An immune response to Skysona may cause rapid loss of efficacy of Skysona in patients with full deletions of the *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 as clinical manifestations 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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) (*see Appendix E*);
2. Prescribed by or in consultation with both (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 magnetic resonance imaging (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. One of the following (a or b):
   a. Member has no available HLA (human leukocyte antigen)-matched (i.e., full HLA-matching of all evaluated alleles) donor;
   b. Member has an available HLA-matched donor, and both of the following (i and ii):
      i. Provider submits medical rationale that allogeneic hematopoietic stem cell transplantation (HSCT) is not feasible (e.g., donor unable to undergo donation procedure because of medical impairments);
      ii. Member understands the risks and benefits of alternative therapeutic options such as allogeneic HSCT;
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 or gene therapy;
10. 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 F for examples*);
11. Member is not positive for the presence of HIV type 1 or 2;
12. Dose contains a minimum of 5×10^6 CD34+ cells per kg.

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

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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.

*Appendix E: VLCFA Reference Ranges**

VLCFAs	Normal Levels	Males with ALD
C26:0 µmol/L	0.67 +/- 0.13	2.94 +/- 0.87
C24:0/C22:0 ratio	0.86 +/- 0.13	1.52 +/- 0.21
C26:0/C22:0 ratio	0.01 +/- 0.003	0.05 +/- 0.02

**VLCFA lab reference ranges may vary*

Appendix F: Baseline Hematologic Assessments
- 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.; September 2022. Available at: https://www.fda.gov/media/161640/download. Accessed September 19, 2022.
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 September 19, 2022.
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 September 19, 2022.

4. 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.
5. Zhu J, Eichler F, Biffi A, et al. The changing face of adrenoleukodystrophy. Endocr Rev. 2020 August;41(4):577-593.
6. ALD Info. Diagnosis of ALD. Available at: https://adrenoleukodystrophy.info/clinical-diagnosis/diagnosis-of-ald. Accessed August 4, 2021.

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 FDA labeling; clarified that Skysona is indicated to be dosed one time only in Section II; references reviewed and updated.	10.11.22	11.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.