Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the
Blue Cross Blue Shield Association

Title: Skysona (elivaldogene autotemcel)

Professional / Institutional
Original Effective Date: November 15, 2022
Latest Review Date: May 14, 2024
Current Effective Date: December 22, 2022

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Skysona® (elivaldogene autotemcel) Suspension for intravenous infusion	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 less than or equal to 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores 0.5-9		1

See package insert for FDA preshttps://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Adrenoleukodystrophy	Adrenoleukodystrophy is a peroxisomal disorder resulting from abnormal metabolism of the very-long-chain fatty acids (VLCFA). It is classified into different subtypes based on the mode of inheritance, clinical presentation, age of onset, and organs involved. The prognosis is poor, and the majority of affected patients will develop neurological disabilities and death.(2) Adrenoleukodystrophy (ALD) is a genetic disorder that follows X linked inheritance pattern in most cases (X-ALD). A unique neonatal form classified as one form of Zellweger syndrome has an autosomal recessive inheritance pattern (N-ALD). The brain, spinal cord, adrenal glands, and testes are the most commonly affected organs. Given the multiple organs, involvement multidisciplinary team approach is highly recommended in the management plan.(2) X-ALD disease has links with the ABCD1 gene mutation. ABCD1 gene plays a significant role in the very-long-chain fatty acids (VLCFA)s transport system in the peroxisomes, where VLCFAs can undergo further metabolism. The abnormal ABCD1 gene mutation interferes with this process and results in abnormal accumulation of VLCFA in different body organs and subsequently interferes with the organs' normal physiological function. A mutation causes the neonatal form in any of the PTS1 receptor, PXR 1, PEX1, PEX 10 or PEX 13 genes. Four main subtypes of ALD have been described based on organs affected and age of presentation(2): • Neonatal • Childhood cerebral form • Adrenomyeloneuropathy • Adrenal insufficiency Central nervous system pathological findings in ALD consist of symmetrical demyelination of the white matter. These effects commonly occur in the corpus callosum and the occipitoparietal region. In severe cases, the spinal cord may get affected. At the cellular level, swelling and vacuolization are caused by infiltrates of active inflammatory cells (macrophages and astrocytes). These changes usually result in the loss of the myelin sheets, oligodendrocytes, and neuronal axons. Ultimately dystrophic mineralization is seen on the histological examination. X-ALD usually has three phenotypes, classified based on the age of presentation and the organs affected(2): • Childhood cerebral ALD, typically affect children between the age of three to ten years. The hallmark feature that characterizes this form is developmental regression. More progressive sensory and severe neurological deficits, severe disability, coma, and death are generally followed by more progressive sensory and severe neurological deficits. A small percentage of adults may present in a similar pattern to the childhood cerebral ALD. • Addison disease. The adrenal gland dysfunction characterizes this form. The manifestations associated with this subtype are the result of decreased production of: o Aldosterone (hyponatremia, fatigue, hypotension, dehydration)

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Cortisol (hypoglycemia and generalized weakness)
Hyperpigmentation of the skin may also occur.

Adrenomyeloneuropathy; the typical age of presentation is in the third decade of life. It presents a milder spectrum of ALD. Walking difficulties, unbalanced gait, and bowel/bladder sphincter dysfunction are typical manifestations.

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<tr><td>Cerebral adrenoleukodystrophy neurologic function scale</td><td>The cerebral adrenoleukodystrophy neurologic function scale is used to evaluate gross clinical neurologic status.(3)
<table>
<tr><td>Hearing/auditory processing problems</td><td>1</td></tr>
<tr><td>aphasia/apraxia</td><td>1</td></tr>
<tr><td>Loss of communication</td><td>3</td></tr>
<tr><td>Vision impairment/fields cut</td><td>1</td></tr>
<tr><td>Cortical blindness</td><td>2</td></tr>
<tr><td>Swallowing difficulty or other central nervous system dysfunction</td><td>2</td></tr>
<tr><td>Tube feeding</td><td>2</td></tr>
<tr><td>Running difficulties/hyperreflexia</td><td>1</td></tr>
<tr><td>Walking difficulties/spasticity/spastic gait (no assistance)</td><td>1</td></tr>
<tr><td>Spastic gait (needs assistance)</td><td>2</td></tr>
<tr><td>Wheelchair required</td><td>2</td></tr>
<tr><td>No voluntary movement</td><td>3</td></tr>
<tr><td>Episodes of urinary or fecal incontinency</td><td>1</td></tr>
<tr><td>Total urinary or fecal incontinency</td><td>2</td></tr>
<tr><td>nonfebrile seizures</td><td>1</td></tr>
<tr><td>Possible total score</td><td>25</td></tr>
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</td></tr>
<tr><td>Loes Score</td><td>The Loes score is a MRI severity scale scoring system. A severity score (0 to 34) is calculated for each MRI scan based on a point system derived from location and extent of involvement and the presence of focal and/or global atrophy.(4)

Loes MRI severity scale scoring - each region is given a score of 0 for normal, 0.5 for unilateral involvement, and 1 for bilateral involvement or atrophy.(5)

Parieto-occipital white matter (maximum 4)
Anterior temporal white matter (maximum 4)
Frontal white matter (maximum 4)

Periventricular
Central
Subcortical
Local atrophy

Corpus callosum (maximum 5)

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	○ Splenium ○ Genu ○ Body ○ Splenium atrophy ○ Genu atrophy • Global atrophy (maximum 4) ○ Mild ○ Moderate ○ Severe ○ Brainstem • Basal ganglia (maximum 1) • Visual pathway (maximum 4) ○ Optic radiation ○ Meyer's loop ○ Lateral geniculate body ○ Optic tract • Auditory pathway (maximum 4) ○ Medial geniculate body ○ Brachium of inferior colliculus ○ Lateral lemniscus ○ Pons • Cerebellum (maximum 2) ○ White matter ○ Atrophy • Projection fibers (maximum 2) ○ Internal capsule ○ Brain stem
Efficacy	Elivaldogene autotemcel was studied in a Phase 2/3 interventional clinical trial with 32 participants (ALD-102; NCT01896102). Inclusion criteria included male children up to 17 years of age with a diagnosis of active cerebral adrenoleukodystrophy (ALD) and a neurologic function score (NFS) of less than or equal to 1.(6) Exclusion criteria included(6): • Receipt of an allogeneic transplant or gene therapy • Availability of a willing 10/1- HLA-matched sibling donor (excluding female heterozygotes) • Use of statins, Lorenzo's Oil, or dietary regimens used to lower very long chain fatty acids (VLCFA) levels (participants must discontinue use of these medications at time of consent) • Any conditions that make it impossible to perform MRI studies • Hematological compromise as evidenced by: ○ Peripheral blood absolute neutrophil count (ANC) less than 1500 cells/mm^3 ○ Platelet count less than 100,000 cells/mm^3, or ○ Hemoglobin less than 10 g/dL ○ Uncorrected bleeding disorder • Hepatic compromise as evidenced by: ○ Aspartate transaminase (AST) value greater than 2.5 X the upper limit of normal (ULN) ○ Alanine transaminase (ALT) value greater than 2.5 X ULN ○ Total bilirubin value greater than 3.0 mg/dL, except if there is a diagnosis of Gilbert's Syndrome and the participant is otherwise stable

	• Renal compromise as evidenced by abnormal renal function (actual or calculated creatinine clearance less than 50 mL/min • Cardiac compromise as evidenced by left ventricular ejection fraction less than 40% • Immediate family member with a known or suspected Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome, and familial adenomatous polyposis) • Clinically significant active bacterial, viral, fungal, parasitic, or prion-associated infection • Positive for human immunodeficiency virus type 1 or 2 (HIV-1, HIV-2); hepatitis B; hepatitis C; human T lymphotropic virus 1 (HTLV-1). (participants who have been vaccinated against hepatitis B [hepatitis B surface antibody-positive] who are negative for other markers of prior hepatitis B infection [e.g., negative for hepatitis B core antibody (Ab)] were eligible. Participants with past exposure to hepatitis B virus (HBV [HBcAb positive and/or HBeAb positive]) were also eligible provided they have a negative test for HBV DNA. Participants who are positive for anti-hepatitis C antibody are eligible as long as they have a negative hepatitis C viral load • Any clinically significant cardiovascular or pulmonary disease, or other disease or condition that would be contraindicated for any of the other study procedures • Absence of adequate contraception for fertile participants. Male participants and their female partners were required to use two different effective methods of contraception from screening through at least 6 months after drug product infusion • Any contraindications to the use of granulocyte colony stimulating (G-CSF) during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan or cyclophosphamide, including known hypersensitivity to the active substances or to any of the excipients in the formulations The primary outcome was the percentage of participants who were alive and have none of the 6 major functional disabilities (MFDs) at Month 24 and without allo-HSCT or rescue cell administration. The 6 MFDs consisted of loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, complete loss of voluntary movement.(6)

REFERENCES

Number	Reference
1	Skysona prescribing information. bluebird bio, Inc. September 2022.
2	Alsaleem M, Saadeh L. Adrenoleukodystrophy. [Updated 2021 Nov 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562328/
3	Miller WP, Mantovani LF, Muzic J, Rykken JB, Gawande RS, Lund TC, Shanley RM, Raymond GV, Orchard PJ, Nascene DR. Intensity of MRI Gadolinium Enhancement in Cerebral Adrenoleukodystrophy: A Biomarker for Inflammation and Predictor of Outcome following Transplantation in Higher Risk Patients. AJNR Am J Neuroradiol. 2016 Feb;37(2):367-72. doi: 10.3174/ajnr.A4500. Epub 2015 Oct 1. PMID: 26427835; PMCID: PMC5177792.
4	Loes DJ, Hite S, Moser H, er al. Adrenoleukodystrophy: A Scoring Method for Brain MR Observations. AJNR AM J Neuroradiol 15:1761-1766, Oct 1994.

Number	Reference
5	Kumar S, Sait H, Polipalli SK, Pradhan GS, Pruthi S, Kapoor S. Loes Score: Clinical and Radiological Profile of 22 Patients of X-Linked Adrenoleukodystrophy: Case Series from a Single Center. Indian J Radiol Imaging. 2021 Apr;31(2):383-390. doi: 10.1055/s-0041-1734366. Epub 2021 Jul 28. PMID: 34556923; PMCID: PMC8448211.
6	Bluebird Bio. A study of the Efficacy and Safety of Hematopoietic Stem Cells Transduced With Lenti-D Lentiviral Vector for the Treatment of Cerebral Adrenoleukodystrophy (CALD). ClinicalTrials.gov Identifier: NCT: 01896102.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) 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 of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J3590	Skysona	elivaldogene autotemcel iv susp		M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Skysona	elivaldogene autotemcel iv susp		Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of active cerebral adrenoleukodystrophy (ALD) as defined by BOTH of the following: A. Elevated very long chain fatty acids (VLCFA) values **AND** B. Active central nervous system (CNS) disease established by central radiographic review of brain magnetic resonance imaging (MRI) demonstrating: 1. Loes score between 0.5 and 9 (inclusive) on the 34-point scale **AND** 2. Gadolinium enhancement on MRI of demyelinating lesions **AND** 2. The patient has a Neurologic Function Score (NFS) less than or equal to 1 **AND** 3. ONE of the following: A. The patient's sex is male **OR** B. The requested agent is medically appropriate for the patient's sex **AND** 4. If the patient has an FDA labeled indication, then ONE of the following: The patient 's age is within FDA labeling for the requested indication for the requested agent **OR** There is support for the use of the requested agent for the patient's age for the requested indication 5. The patient has NOT had an allogeneic hematopoietic stem cell transplant **AND** 6. The patient does NOT have availability of a willing 10/10 HLA-matched sibling donor (excluding female heterozygotes) **AND** 7. The patient does NOT have any of the following indicators of hematological compromise: A. Peripheral blood absolute neutrophil count (ANC) less than 1500 cells/mm^3 B. Platelet count less than 100,000 cells/mm^3 C. Hemoglobin less than 10 g/dL D. Uncorrected bleeding disorder **AND** 8. The patient does NOT have any of the following indicators of hepatic compromise: A. Aspartate transaminase (AST) value greater than 2.5 X the upper limit of normal (ULN) B. Alanine transaminase (ALT) value greater than 2.5 X ULN C. Total bilirubin value greater than 3.0 mg/dL unless the patient has a diagnosis of Gilbert's Syndrome and is otherwise stable **AND** 9. The patient does NOT have hepatitis B **AND** 10. The patient is NOT HIV positive **AND** 11. ONE of the following: A. The patient's hepatitis C virus (HCV) antibody is negative **OR** B. The patient's HCV antibody is positive AND the patient's HCV RNA is negative **AND** 12. The patient does NOT have another active infection **AND** 13. The patient has NOT had previous gene therapy for any diagnosis **Length of Approval**: 1 course per lifetime

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

REVISIONS	
11-15-2022	Policy added to the bcbsks.com web site. Policy maintained by Prime Therapeutics LLC
07-25-2023	Policy reviewed by Prime Therapeutics LLC with no revisions.
05-14-2024	Policy reviewed by Prime Therapeutics LLC with no revisions.