Drug Coverage Policy

Effective Date.....1/08/2026
Coverage Policy Number.....IP0529
Policy Title.....Skysona

Neurology - Gene Therapy - Skysona

- Skysona® (elivaldogene autotemcel intravenous infusion – Bluebird Bio)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Skysona, an autologous hematopoietic stem cell-based gene therapy, is indicated to slow the progression of neurologic dysfunction in boys 4 years to 17 years of age with early, active cerebral adrenoleukodystrophy without an available human leukocyte antigen (HLA)-matched donor for

allogeneic hematopoietic stem cell transplant (HSCT).[1] Early, active cerebral adrenoleukodystrophy refers to asymptomatic or mildly symptomatic (neurologic function score ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging and Loes scores of 0.5 points to 9 points. This indication was 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 confirmatory trials. Skysona is given as a single dose by intravenous infusion; the minimum recommended dose is 5.0×10^6 CD34+ cells/kg.

Disease Overview
Cerebral adrenoleukodystrophy is a severe form of adrenoleukodystrophy, a rare, neurodegenerative X-linked genetic disease.[2-4] It is caused by a defect in the adenosine triphosphate-binding cassette, subfamily D, member 1 (*ABCD1*) gene.[2] Mutations in *ABCD1* lead to abnormal breakdown of very long chain fatty acids which accumulate and predominantly impact adrenal and nervous system tissues. This inflammatory cerebral phenotype is noted most commonly in young males,[2,3] with the onset commonly occurring in those between 4 years and 10 years in age.[4] However, cerebral adrenoleukodystrophy can occur in adulthood. A patient with cerebral adrenoleukodystrophy will experience rapid progressive impairments impacting cognition, behavior, speech, vision, and hearing, as well as motor function. If therapies are not received, such allogeneic HSCT, profound disability or death may occur.[2-4] Reviews provide additional information regarding monitoring and diagnosis for this condition (e.g., Loes and neurologic function scores).[5-8]

Clinical Efficacy
The efficacy of Skysona was evaluated in two 24-month, open-label, single-arm, single-dose, multicenter, multinational pivotal trials involving male patients ≤ 17 years of age with early, active cerebral adrenoleukodystrophy as defined by its FDA-approved indication.[1,2] STARBEAM (ALD-102), a Phase II/III investigation, involved 32 patients; some results are published.[2] Study 2 (ALD-104) included 35 patients.[1] Skysona was compared with a natural history population, as well as patients who underwent allogeneic HSCT.[1,2] Patients involved in these two studies had elevated very long chain fatty acid levels and confirmed mutations in the *ABCD1* gene.[1] Skysona therapy led to a slower progression to the first MFD or death (MFD-free survival) from the time of symptom onset for patients with early, active cerebral adrenoleukodystrophy compared with a similar natural history population. Of note, MFDs were defined as follows: loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.

Guidelines
Skysona has not been addressed in guidelines following approval by the FDA. International recommendations for the diagnosis and management of patients with adrenoleukodystrophy (a consensus-based approach) are available which were published in 2022.[9] It was noted that allogeneic HSCT is the standard treatment for cerebral adrenoleukodystrophy and can halt progression. Genetically transduced autologous stem cell transplantation (gene therapy [Skysona]) should be considered in boys if allogeneic donor options are poor. Outcome is poor in patients with advanced disease (Loes score > 9 and/or a neurologic function score > 1). Regarding gene therapy (Skysona), it states that this therapy is not available for routine care; long-term safety data are not yet available. Treatment for boys or men with advanced disease or progressive lesions without gadolinium enhancement should only be considered after careful assessment in experienced centers.

Safety
Skysona has a Boxed Warning regarding hematologic malignancy.[1] Hematologic malignancies, including life-threatening cases of myelodysplastic syndrome and acute myeloid leukemia, have

developed in patients who received Skysona. Patients have been diagnosed between 14 months and 10 years following receipt of Skysona; the cancers appear to be due to Skysona therapy. Monitor patients for evidence of malignancy. As of July 2025, 15% of Skysona clinical study patients (n = 10/67) have been diagnosed with hematologic malignancies.[1] Published data from some cases are available.[10]

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for benefit coverage of Skysona. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skysona as well as the specialized training required for administration of Skysona, approval requires Skysona to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 6 months to allow for an adequate time frame to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria, as noted by **[verification in claims history required]**. For dosing criteria verification of the appropriate weight-based dosing is required by the Medical Director as noted by **[verification required]**. In the criteria for Skysona, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Skysona as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, medical test results, claims records, prescription receipts, and/or other information. All documentation must include patient-specific identifying information.

Skysona is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Cerebral Adrenoleukodystrophy.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, and S):
   - **A)** Patient is male*; AND
   - **B)** Patient is ≥ 4 and < 18 years of age; AND
   - **C)** Patient has not received Skysona in the past **[verification in claims history required]**; AND
     Note: If no claim for Skysona is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Skysona.
   - **D)** Patient has early, active cerebral adrenoleukodystrophy as demonstrated by meeting ALL of the following (i, ii, and iii):
     - **i.** Patient has a neurologic function score ≤ 1 **[documentation required]**; AND
     - **ii.** Patient has gadolinium enhancement on brain magnetic resonance imaging (MRI) **[documentation required]**; AND
     - **iii.** Patient has a Loes score between 0.5 and 9 **[documentation required]**; AND
   - **E)** Patient has a pathogenic variant in the adenosine triphosphate binding cassette, sub family D member 1 (*ABCD1*) gene **[documentation required]**; AND
   - **F)** Patient has elevated very long chain fatty acid levels according to the standard reference values of the laboratory **[documentation required]**; AND
   - **G)** Patient meets ONE of the following (i or ii):

i. Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR
ii. Patient has an HLA-matched donor, but the individual is not able or is not willing to donate; AND

H) Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND

I) Patient does not have any of the following (i and ii):
i. Prior or current hematologic malignancy or myeloproliferative disorder; AND
ii. Familial cancer syndrome or a history of such in his immediate family; AND

J) According to the prescribing physician, hematopoietic stem cell transplantation is appropriate for the patient; AND

K) Patient has undergone liver function testing within the past 30 days and meets ALL of the following (i, ii, and iii):
i. Aspartate aminotransferase level is ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
ii. Alanine aminotransferase level is ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
iii. Total bilirubin level is ≤ 3.0 mg/dL **[documentation required]**; AND

L) Within the past 30 days, the patient meets ONE of the following (i or ii):
i. Estimated creatinine clearance is ≥ 50 mL/minute **[documentation required]**; AND
ii. Estimated glomerular filtration rate is ≥ 70 mL/minute/1.73 m^2 **[documentation required]**; AND

M) According to the prescribing physician, patient does not have evidence of cardiac compromise; AND

N) Prior to collection of cells for manufacturing, screening is negative for ALL of the following (i, ii, iii, and iv):
i. Hepatitis B virus **[documentation required]**; AND
ii. Hepatitis C virus **[documentation required]**; AND
iii. Human T-lymphotropic virus 1 and 2 **[documentation required]**; AND
iv. Human immunodeficiency virus 1 and 2 **[documentation required]**; AND

O) Within the past 30 days, the patient meets ALL the following (i, ii, and iii):
i. Peripheral blood absolute neutrophil count ≥ 1,500 cells/mm^3 **[documentation required]**; AND
ii. Platelet count ≥ 100,000 cells/mm^3 **[documentation required]**; AND
iii. Hemoglobin ≥ 10 g/dL **[documentation required]**; AND

P) Patient meets ALL of the following (i, ii, iii, and iv):
i. Patient will undergo mobilization, apheresis, myeloablative conditioning, and lymphodepletion; AND
ii. A granulocyte-colony stimulating factor product will be used for mobilization; AND
iii. Busulfan will be used for myeloablative conditioning; AND
iv. Cyclophosphamide or fludarabine will be used for lymphodepletion; AND

Q) Medication is prescribed by a hematologist, a neurologist, and/or a stem cell transplant specialist

R) Current patient body weight has been obtained within the past 30 days **[documentation required]**; AND

S) If criteria A through R are met, approve one dose of Skysona by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0 x 106 CD34+ cells/kg of body weight **[verification required]**.

* Refer to the Policy Statement.

Dosing. The recommended dose is a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight administered by intravenous infusion.

Conditions Not Covered

Skysona for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Patient has a Full *ABCD1* Gene Deletion.** In one patient involved in the Skysona clinical trials who had a full *ABCD1* gene deletion, disease progression occurred.[1] The patient experienced radiologic disease progression, along with declining peripheral blood vector copy number, suggesting a loss of efficacy which may have been immune mediated. A noted limitation of use for Skysona is that an immune response to Skysona may limit the persistence of descendent cells of Skysona, leading to rapid loss of efficacy of in patients with full deletions of the *ABCD1* gene.

2. **Prior Hematopoietic Stem Cell Transplantation.**
   Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
   Prior allogeneic hematopoietic stem cell transplant was an exclusion criterion in the pivotal studies.

3. **Prior Receipt of Gene Therapy.** This was an exclusion criterion in the pivotal studies.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals (Code effective until 12/31/2025)
J3387	Injection, elivaldogene autotemcel, per treatment
J3490	Unclassified drugs (Code effective until 12/31/2025)
J3590	Unclassified biologics (Code effective until 12/31/2025)

References

1. Skysona® intravenous infusion [prescribing information]. Sommerville, MA: Bluebird Bio; August 2025.
2. Eichler F, Duncan CN, Musolino PL, et al. Lentiviral gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med*. 2024;391(14):1302-1312.
3. Raymond GV, Moser AB, Fatemi A. X-Linked Adrenoleukodystrophy. 1999 Mar 26 [Updated 2023 Apr 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1315/pdf/Bookshelf_NBK1315.pdf. Accessed on December 12, 2025.

4. Kornbluh AB, Baldwin A, Fatemi A, et al. Practical approach to longitudinal neurologic care of adults with X-linked adrenoleukodystrophy and adrenomyeloneuropathy. *Neurol Genet*. 2024;10:e200192.
5. Kumar S, Sait H, Polipalli SK, et al. Loes score; clinical and radiological profile of 22 patients of X-linked adrenoleukodystrophy: case series from a single center. *Indian J Radiol Imaging*. 2021;31(2):383-390.
6. Loes DJ, Site S, Moser H, et al. Adrenoleukodystrophy: a score method of brain MR observations. *AJNR Am J Neuroradiol*. 1994;15:1761-1766.
7. Thibert KA, Raymond GV, Nascene DR, et al. Cerebrospinal fluid matrix metalloproteinases are elevated in cerebral adrenoleukodystrophy and correlated with MRI severity and neurologic dysfunction. *PLoS One*. 2012;7(11):e50430.
8. 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*. 2000;31(5):227-239.
9. Engelen M, Van Ballegoij WJ, 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.
10. Duncan CN, Bledsoe JR, Grzywacz B, et al. Hematologic cancer after gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med*. 2024;391:1287-1301.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	5/1/2024
Annual Revision	**Added** "Policy Statement" to the policy **Added** "**Documentation:** Documentation is required for use of Skysona as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, medical test results, claims records, prescription receipts, and/or other information." **Cerebral Adrenoleukodystrophy:** • **Updated** criteria **from** "age 4 years to 17 years" **to** "Patient is ≥ 4 and < 18 years of age." • **Added** criteria "Patient has not received Skysona in the past [verification in claims history required] and **added** "Note: If no claim for Skysona is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Skysona." • **Updated** criteria **from** "Documentation of adrenoleukodystrophy as demonstrated by meeting genetic confirmation of a pathogenic variant, or likely pathogenic variant, in the adenosine triphosphate binding cassette, sub family D member 1 (*ABCD1*) gene" **to** "Patient has a pathogenic variant in the adenosine triphosphate binding cassette, sub family D	1/16/2025

	member 1 (ABCD1) gene [documentation required]." • **Updated** criteria **from** "According to the prescriber, is unable to receive stem cell transplant due to no matching, or unwilling, Human Leukocyte Antigen (HLA)-Matched family donor" **to** "Patient meets ONE of the following (i or ii): i. Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR ii. Patient has an HLA-matched donor, but the individual is not able or is not willing to donate." • **Updated** criteria **from** "Prescriber attestation of the following: No active bacterial, viral, fungal or parasitic infection" **to** "Patient does not currently have an active bacterial, viral, fungal, or parasitic infection." • **Updated** criteria **from** "Prescriber attestation of the following: No prior or current malignancy or myeloproliferative disorder; No familial cancer syndrome or a history of such in their immediate family" **to** "Patient does not have any of the following (i and ii): i. Prior or current hematologic malignancy or myeloproliferative disorder; AND ii. Familial cancer syndrome or a history of such in his immediate family." • **Updated** criteria **from** "According to the prescriber, hematopoietic stem cell transplantation procedure is appropriate for the individual as required to receive Skysona gene therapy" **to** "According to the prescribing physician, hematopoietic stem cell transplantation is appropriate for the patient." • Regarding the requirement that the patient has "adequate hepatic function" this wording was changed to state that the patient has "undergone liver function testing." Also, the requirement that this information be obtained "within the past 30 days" was added. For the laboratory requirements, the phrase "values are normal or" was changed to "level is." • Regarding the requirement that the patient has "adequate renal function," this phrase was removed before the cited estimated creatinine clearance and estimated glomerular filtration rate. Also, the requirement that this information be obtained "within the past 30 days" was added. • **Updated** criteria **from** "Documentation of Adequate cardiac function as evidenced by a left ventricular ejection fraction greater than 40%" **to** "According to the prescribing physician, patient does not have evidence of cardiac compromise." • The phrase "Adequate hematological function as evidenced by ALL the following:" was removed	

	before the cited hematologic laboratory requirements. Also, the requirement that this information be obtained "within the past 30 days" was added. The requirement that the patient does not have an uncorrected bleeding disorder was removed. • **Added** the criteria "Patient meets ALL of the following (i, ii, iii, and iv): i. Patient will undergo mobilization, apheresis, myeloablative conditioning, and lymphodepletion; AND ii. A granulocyte-colony stimulating factor product will be used for mobilization; AND iii. Busulfan will be used for myeloablative conditioning; AND iv. Cyclophosphamide or fludarabine will be used for lymphodepletion." • A specific individual criterion was added that current patient body weight has been obtained within the past 30 days with documentation required. • **Added** the criteria "If criteria A through R are met, approve one dose of Skysona by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight." • Dosing criteria were rephrased to emphasize that Skysona is provided as a "one-time (per lifetime)" single dose. The requirement that the body weight be obtained based on patient weight prior to the first apheresis was removed. It was added that verification is required. **Authorization Duration:** **Updated** criteria **from** "Authorization is for a one-time treatment for 6 months" **to** "Approve for a one-time (per lifetime) single dose."	
Selected Revision	**Coding Information** **Added** HCPCS: J3397 with a note "Code effective 1/1/2026" **Updated** the description for C9399, J3490 & J3590 to include the note "Code effective until 12/31/2025"	12/15/2025
Annual Revision	**Updated** policy template. **Coding Information** **Removed** "Code effective 1/1/2026" from HCPCS J3397	1/08/2026

The policy effective date is in force until updated or retired.