Drug Coverage Policy

Effective Date.....1/16/2025
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 and have discretion in making individual coverage determinations. 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.

Cigna Healthcare Coverage Policy

OVERVIEW
Skysona, an autologous hematopoietic stem cell-based gene therapy, is indicated to slow the progression of neurologic dysfunction in boys 4 to 17 years of age with early, active **cerebral adrenoleukodystrophy**.[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 (MRI) and Loes scores of 0.5 to 9 points.[1] This indication was approved under accelerated approval based on 24-month Major Functional Disability-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 x 10^6 $CD34^+$ cells/kg.

Disease Overview

Cerebral adrenoleukodystrophy is a rare, neurodegenerative X-linked genetic disease in young boys that mainly affects the nervous system and adrenal glands.[2-6] The estimated incidence of adrenoleukodystrophy is 1:20,000 to 1:30,000 males. It is caused by a defect in the adenosine triphosphate-binding cassette, subfamily D, member 1 (*ABCD1*) gene. Very long chain fatty acids accumulate, which causes inflammation and damage to the brain; other tissue types are also impacted. Among patients diagnosed with adrenoleukodystrophy, cerebral adrenoleukodystrophy developed in around 35% of boys before 12 years of age; a small percentage of impacted patients are ≥ 12 years of age. The conditions leads to progressive destruction of white matter, loss of cognitive and neurologic function, and early death if not treated.[2] Early stages of cerebral adrenoleukodystrophy are clinically asymptomatic and are only detected by performing an MRI of the brain.[2-4] Irreversible, devastating neurologic decline can result which include major functional disabilities such as loss of communication, cortical blindness, dependence on tube feeding, total incontinence, use of a wheelchair for ambulation, or complete loss of voluntary movement. As the disease progresses, patients often develop profound disability.[2-4] If an allogeneic hematopoietic stem cell transplantation (HSCT) is not performed, almost one-half of impacted patients will likely die within a decade after symptom onset.[2]

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) was a Phase II/III investigation which is completed and involved 32 patients who did not have a matched sibling donor for allogeneic HSCT.[1,2] Study 2 (ALD-104) is an ongoing trial that included 35 patients.[1] Skysona was compared with a natural history population, as well as patients who underwent allogeneic HSCT. Patients in both studies could enroll in a long-term follow-up study (LTF-304).[1,2] It should be noted that patients involved in these two studies had elevated very long chain fatty acid levels and confirmed mutations in the *ABCD1* gene. In STARBEAM study, 91% of patients (n = 29/32) completed the 24-month study and are being followed long-term. At Month 24, none of these patients had major functional disabilities and overall survival was 94%. At a median of 6 years of follow-up, the neurologic function score was stable compared with the baseline score in most patients (n = 30/32); 81% of patients had no major functional disabilities.

Guidelines
Skysona has not been addressed in guidelines post FDA-approval. In September 2022, international recommendations for the diagnosis and management of patients with adrenoleukodystrophy (a consensus-based approach) were published.[7] 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 (if available) in boys if allogeneic donor options are poor. Outcome is poor in patients with advance 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 7.5 years of age following receipt of Skysona, and the cancers appear to be due to the Skysona lentiviral vector, Lenti-D, integration in proto-oncogenes. Due to the risk of hematologic malignancy, consider alternative therapies, including allogeneic HSCT for patients who have a suitable, willing, and available matched sibling donor before treating a child with Skysona.[1] As of April 2024, hematologic cancer developed in 9% of patients (n = 7/67) who received Skysona in ALD-102 and

ALD-104.[8] At diagnosis, all patients had high-frequency integrations in oncogenes, most of which were *MECOM*.

Medical Necessity Criteria

POLICY STATEMENT

Prior Authorization is recommended 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.

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

Any other use is considered experimental, investigational or unproven, 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.[1,9] The patient experienced radiologic disease progression, along with declining peripheral blood vector copy number, suggesting a loss of product efficacy which may have been immune mediated. The patient eventually underwent allogeneic HSCT for treatment. A noted limitation of use is that 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 *ABCD1* transgene.

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
J3490	Unclassified drugs
J3590	Unclassified biologics

References

1. Skysona® intravenous infusion [prescribing information]. Sommerville, MA: Bluebird Bio; April 2024.
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 1, 2024.
4. X-linked cerebral adrenoleukodystrophy. National Institute of Health: Genetic and Rare Disease Information Center Website. Available at: https://rarediseases.info.nih.gov/diseases/9412/x-linked-cerebral-adrenoleukodystrophy. Last updated September 2024. Accessed on December 1, 2024.
5. 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.

6. Engelen M, Kemp S, Eichler F. Adrenoleukodystrophy. *Handb Clin Neurol*. 2024;204:133-138.
7. 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.
8. Duncan CN, Bledsoe JR, Grzywacz B, et al. Hematologic cancer after gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med*. 2024;391:1287-1301.
9. Lund TC, Orchard PJ, Nascene DR, et al. Secondary failure of lentiviral vector gene therapy in a cerebral adrenoleukodystrophy patient with an ABCD1 whole-gene deletion. *Mol Ther*. 2024;32(10):3313-3317.

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 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."	1/16/2025

	• **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 x 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."	

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