UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Gene Therapy – Skysona Utilization Management Medical Policy
- Skysona® (elivaldogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 11/02/2022

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 [NFS] ≤ 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 (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 rare, neurodegenerative X-linked genetic disease in young boys that mainly affects the nervous system and adrenal glands.[2-4] 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 in and damage to the brain; other tissue types are also impacted. Around 40% of patients with adrenoleukodystrophy will develop cerebral adrenoleukodystrophy which is associated with rapid, progressive cerebral demyelination which usually occurs when patients are 3 to 12 years of age. Early stages of cerebral adrenoleukodystrophy are clinically asymptomatic and are only detected by performing an MRI of the brain. Irreversible, devastating neurologic decline can result which include MFDs 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. If an allogeneic hematopoietic stem cell transplantation (HSCT) is not performed, almost one-half of impacted patients will likely die within 5 years of symptom onset.

Clinical Efficacy

The efficacy of Skysona was assessed 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.[1,5,6] STARBEAM (ALD-102) [published data in 17 patients] {n = 32} was a Phase II/III investigation which is completed and involved patients who did not have a matched sibling donor for allogeneic HSCT. Study 2 (ALD-104) [unpublished] {n = 35} is an ongoing study and patients with a matched sibling donor for allogeneic HSCT could participate. 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). 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 the published STARBEAM study, at time of the interim analysis (April 2017), a total of 17 boys had received Skysona with a median follow-up of 29.4 months (range 21.6 to 42.0 months). In total, 88% of patients (n = 15/17) who received Skysona were alive and free of an MFD; all maintained an NFS score of 0 to 1.[5] In the symptomatic Skysona subpopulation (n = 11), slower progression to MFD or death (MFD-free survival) from time of symptom onset (first NFS ≥ 1) was observed compared with a similar natural history population (n = 7).[1] Data involving the entire efficacy population (n = 61) analyzed overall survival compared to early, active allogeneic HSCT subpopulations by various donor type (human

leukocyte antigen [HLA]-matched allogeneic HSCT subpopulation [n = 34] and HLA-mismatched allogeneic HSCT subpopulation [n = 17]). A reduced overall survival was noted in the first 9 months after treatment among the subpopulation who received allogeneic HSCT from an HLA-mismatched donor compared with Skysona, as well as the group who received an allogeneic HSCT from an HLA-matched donor (results presented graphically). The earlier mortality in the HLA-mismatched allogeneic HSCT subpopulation was mainly due to allogeneic HSCT-related toxicities.

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 treatment of 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 NFS > 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.

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 dose per lifetime. The approval duration is 6 months to allow for an adequate time frame to prepare and administered one dose of therapy. For certain criteria, attestation is required as noted by **[attestation required by physician]**. 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. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

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, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Skysona is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cerebral Adrenoleukodystrophy.** Approve a one-time (lifetime) dose if the patient meets the following criteria (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, and S).
   - **A)** Patient is a male*; AND
   - **B)** Patient is ≥ 4 and < 18 years of age; AND
   - **C)** Patient has early, active cerebral adrenoleukodystrophy as demonstrated by meeting 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
   - **D)** Patient has a confirmed mutation in the adenosine triphosphate binding cassette, sub family D member 1 (*ABCD1*) gene **[documentation required]**; AND
   - **E)** Patient has elevated very long chain fatty acid levels according to the standard reference values of the laboratory **[documentation required]**; AND
   - **F)** Patient does not have a Human Leukocyte Antigen (HLA)-matched family donor **[documentation required]**; AND
   - **G)** According to the prescribing physician, the patient is able to undergo monitoring by magnetic resonance imaging; AND
   - **H)** Patient does not currently have an active bacterial, viral, fungal, or parasitic infection as determined by the prescribing physician; 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 adequate hepatic function defined by meeting the following (i, ii, and iii):
     - **i.** Aspartate aminotransferase values are normal or ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
     - **ii.** Alanine aminotransferase values are normal or ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
     - **iii.** Total bilirubin values are normal or ≤ 3.0 mg/dL **[documentation required]**; AND
   - **L)** Patient has adequate renal function as defined by meeting the following (i or ii);
     - **i.** Estimated creatinine clearance is ≥ 50 mL/min; OR
     - **ii.** Estimated glomerular filtration rate is ≥ 70 mL/minute/1.73 m^2; AND
   - **M)** According to the prescribing physician, patient does not have evidence of cardiac compromise; AND
   - **N)** Prior to collection of cells for manufacturing, patient screening is negative for 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)** Prior to therapy, patient does not have evidence of hematological compromise as defined by meeting the following (i, ii, iii, and iv):
     - **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
     - **iv.** Patient does not have an uncorrected bleeding disorder; AND
   - **P)** Patient meets the following (i, ii, iii, and iv):

i. Patient plans to 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) Patient has received or is planning to receive prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome before conditioning; AND
Note: Examples of medications used include ursodeoxycholic acid or Defitelio (defibrotide intravenous infusion).

R) The prescribing physician confirms that the patient or his partner of childbearing potential will be using an effective method of contraception from the start of mobilization through at least 6 months after administration of Skysona; AND

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

* Refer to the Policy Statement.

Dosing. The single dose is given intravenously which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight in which body weight is based on patient weight prior to first apheresis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skysona is not recommended in the following situations:

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. 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 [attestation required by physician]**. 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.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Skysona® intravenous infusion [prescribing information]. Cambridge, MA: Bluebird Bio; September 2022.
2. 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. Created November 8, 2021. Accessed on November 1, 2022.
3. 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/. Accessed on November 1, 2022.
4. Keam SJ. Elivaldogene autotemcel: first approval. *Mol Diagn Ther*. 2021;25(6):803-809.
5. Eichler F, Dunvan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med*. 2017;377(17):1630-1638.
6. Data on File for Skysona. Bluebird Bio. Received November 1, 2022.

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 Sep 29. [Online ahead of print].

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/02/2022