Effective Date **2/1/2023**
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Coverage Policy Number **IP0529**

Elivaldogene autotemcel

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Related Coverage Resources

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. 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

This policy supports medical necessity review for the gene therapy product, elivaldogene autotemcel (Skysona®) intravenous infusion.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Gene Therapy coverage varies across plans. Refer to the customer's benefit plan document for coverage details.

Medical Necessity

Elivaldogene autotemcel (Skysona®) is considered medically necessary for the treatment of Cerebral Adrenoleukodystrophy when the individual meets ALL of the following criteria:

1. Male, age 4 years to 17 years
2. Documentation of adrenoleukodystrophy as demonstrated by meeting **BOTH** of the following:

a. Genetic confirmation of a pathogenic variant, or likely pathogenic variant, in the adenosine triphosphate binding cassette, sub family D member 1 (*ABCD1*) gene
b. Elevated very long chain fatty acid levels according to the standard reference values of the performing laboratory

3. Documentation of early, active cerebral adrenoleukodystrophy as demonstrated by meeting **ALL** of the following:
    a. Neurologic function score (NFS) less than or equal to 1
    b. Gadolinium enhancement (GdE+) on brain magnetic resonance imaging (MRI)
    c. Loes score between 0.5 and 9
4. Documentation of **ALL** of the following:
    a. Adequate hepatic function by meeting **ALL** of the following:
        i. Aspartate aminotransferase values are no greater than 2.5 times the upper limit of normal
        ii. Alanine aminotransferase values are no greater than 2.5 times the upper limit of normal
        iii. Total bilirubin values are no greater than 3.0 mg/dL
    b. Adequate hematological function as evidenced by **ALL** the following:
        i. Peripheral blood absolute neutrophil count of at least 1,500 cells/mm^3
        ii. Platelet count of at least 100,000 cells/mm^3
        iii. Hemoglobin of at least 10 g/dL
        iv. No uncorrected bleeding disorder
    c. Adequate renal function by meeting **ONE** of the following:
        i. Estimated creatinine clearance is at least 50 mL/min
        ii. Estimated glomerular filtration rate is at least 70 mL/minute/1.73 m^2
    d. Adequate cardiac function as evidenced by a left ventricular ejection fraction greater than 40%
    e. Prior to collection of cells for manufacturing, screening for **ALL** of the following is negative:
        i. Hepatitis B virus
        ii. Hepatitis C virus
        iii. Human T-lymphotropic virus 1 and 2
        iv. Human immunodeficiency virus 1 and 2
5. Prescriber attestation of the following:
    a. No active bacterial, viral, fungal or parasitic infection
    b. No prior or current malignancy or myeloproliferative disorder
    c. No familial cancer syndrome or a history of such in their immediate family
6. According to the prescriber, is unable to receive stem cell transplant due to no matching, or unwilling, Human Leukocyte Antigen (HLA)-Matched family donor
7. According to the prescriber, hematopoietic stem cell transplantation procedure is appropriate for the individual as required to receive Skysona gene therapy
8. Medication is prescribed by a hematologist, a neurologist, and/or a stem cell transplant specialist

Dosing for Cerebral Adrenoleukodystrophy. The recommended dose is a single dose, given intravenously, containing a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight in which body weight is based on individual's weight prior to first apheresis.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Authorization Duration

Authorization is for a one-time treatment for 6 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Individual has a Full *ABCD1* Gene Deletion.** In one individual involved in the Skysona clinical trials who had a full *ABCD1* gene deletion, disease progression occurred. The individual 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 individual 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 individuals with full deletions of the *ABCD1* transgene.

2. **Prior Hematopoietic Stem Cell Transplantation**. Allogeneic transplant was an exclusion criterion in the pivotal studies. [5,6]

3. **Prior Receipt of Gene Therapy**. This was an exclusion criterion in the pivotal studies. [5,6]

Coding

This list of codes may not be all-inclusive.

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

Background

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 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.[2-4] 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 less than or equal to 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 greater than 9 and/or NFS greater than 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.

Dosing and Administration[1]
For autologous use only. For intravenous use only.
- Patients must undergo hematopoietic stem cell (HSC) mobilization and apheresis to obtain CD34+ cells for Skysona manufacturing
- Dosing of Skysona is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight
- The minimum recommended dose is 5.0×10^6 CD34+ cells/kg
- Full myeloablative and lymphodepleting conditioning must be administered before infusion of Skysona

Dosage Forms and Strengths[1]
- Skysona is a cell suspension for intravenous infusion
- A single dose of Skysona contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight, suspended in a solution containing 5% dimethyl sulfoxide (DMSO)

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].