09-J4000-33

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Reviewed: 04/09/25

Revised: 01/01/26

Subject: Elivaldogene autotemcel (Skysona) Suspension for Intravenous Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Cerebral adrenoleukodystrophy (CALD) is a rare X-linked genetic disorder caused by mutations in the human adenosine triphosphate binding cassette, sub family D, member 1 (*ABCD1)* transgene. These mutations result in a reduction in adrenoleukodystrophy protein (ALDP) that transport very long-chain fatty acids (VLCFAs) to peroxisomes for metabolism. As a result VLCFAs accumulate within the adrenal gland and cerebral hemispheres of the central nervous system. Patients present with adrenal insufficiency and progressive neurodegenerative disease caused by demyelination. The *ABCD1* gene mutation is estimated to occur in 1 in 17,000 births. Early CALD occurs in male patients age 2 to 10 years and can progress to complete disability within 2 years and death within 4 to 10 years if not treated. Female carriers of the *ABCD1* mutation typically develop less severe symptoms of adrenoleukodystrophy during adulthood.

Glucocorticoids steroids are used for the management of adrenal insufficiency but have no impact on neurological abnormalities. Therefore, allogeneic hematopoietic stem cell transplantation (HSCT) should be considered to limit neurological progression for early-stage disease [e.g., magnetic resonance imaging (MRI) evidence of disease while asymptomatic or minimally symptomatic]. Limitations of HSCT include difficulty identifying a matched donor, as approximately 30% of children with CALD have an HLA-matched sibling donor, and complications of graft rejection and graft-versus-host disease (GvHD) can occur.

Elivaldogene autotemcel (Skysona) is an autologous HSC-based gene therapy that is prepared from the patient's HSCs, which are collected via apheresis procedures. Elivaldogene autotemcel (Skysona) adds functional copies of the *ABCD1* cDNA into patients' HSCs through transduction of autologous CD34+ cells with Lenti-D *lentiviral* vectors (LVV). Following the elivaldogene autotemcel (Skysona) infusion,

transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes (CD14+) capable of producing functional ALDP to slow or possibly prevent further inflammation and demyelination.

According to the manufacturer prescribing information, elivaldogene autotemcel (Skysona) efficacy and safety was evaluated in two 24-month, open-label, single-arm studies in patients with early, active CALD as noted in the prescribing information. However, only one of these studies, STARBEAM ALD-102 (NCT01896102), is complete with interim data published in the literature and the remaining data published in the prescribing information. The STARBEAM ALD-102 study was a single-group, open-label, phase 2/3 study that assessed the efficacy and safety of elivaldogene autotemcel (Skysona) in male patients 17 years of age or younger who had early-stage CALD. The diagnosis of early-stage CALD was established with the following criteria: (1) gadolinium enhancement on MRI due to CALD, (2) a score on the CALD-specific Neurologic Function Scale (which ranges from 0 to 25, with higher scores indicating more severe deficits) of 0 or 1, and (3) a Loes score (which ranges from 0 to 34, with higher scores indicating an increased extent of lesions on MRI) of 0.5 to 9. Additionally, all patients had elevated VLCFAs levels and confirmed mutations in the *ABCD1* gene. Patients with an HLA-matched sibling who could donate cells for transplantation were excluded. The primary outcome was the percentage of patients alive and having no major functional disability at 24 months following the elivaldogene autotemcel (Skysona) infusion. There were 32 male patients enrolled with a median age of 6 years and 53.1% of non-Hispanic or Latino race. The median Loes score was approximately 2 at baseline, and the NFS score was 0 to 1. Based on the primary endpoint, 90.6% of patients who received elivaldogene autotemcel (Skysona) met the efficacy outcome, maintaining a score on the NFS of 0 or 1. Of the three patients not meeting the primary endpoint, one died following rapid disease progression, and two withdrew at the investigator's discretion to receive rescue allogeneic HSCT based on MRI evidence of disease progression; however, these situations were considered not to be treatment-related. No adverse effects related to elivaldogene autotemcel (Skysona) infusion, graft failure, GvHD, or transplantation-related death were observed. Most adverse events occurred in the conditioning phase or first two weeks after infusion and were considered to be consistent with myeloablative chemotherapy.

As outline in the elivaldogene autotemcel (Skysona) prescribing information, the most common non-laboratory adverse reactions (≥ 20%) include mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache, and rash. Additionally, the most common Grade 3 or 4 laboratory abnormalities (≥40%) include leukopenia, lymphopenia, thrombocytopenia, neutropenia, anemia, and hypokalemia.

POSITION STATEMENT:

The administration of elivaldogene autotemcel (Skysona) **meets the definition of medical necessity** when **ALL** of the following are met:

1. Member is a 4 to 17 year old, biological male with a diagnosis of cerebral adrenoleukodystrophy (CALD) at the time of treatment
2. Member has a genetic test demonstrating mutation in the *ABCD1* gene but does not have a full *ABCD1* gene deletion (note: rapid loss of efficacy due to immune response may result with gene deletion) – Laboratory documentation of the genetic testing results must be submitted

3. Member has early, active CALD established by **ALL** of the following:
    a. Elevated very long-chain fatty acids (VLCFAs) levels – Documentation must be submitted
    b. Gadolinuim enhancement on MRI of demyelinating lesions – Documentation must be submitted
    c. Loes score between 0.5 and 9 on the 34-point scale – Documentation must be submitted
    d. Neurologic Function Score (NFS) of 1 or less – Documentation must be submitted
4. Member is clinically stable and able to undergo a hematopoietic stem cell transplant (HSCT) in the opinion of treating physician
5. Member has a negative serologic test for HIV infection (i.e., the member is **NOT** HIV positive)
6. Member does **NOT** have a human leukocyte antigen (HLA)-matched family donor
7. Member will **NOT** use prophylactic HIV anti-retroviral medication within 30 days prior to stem cell mobilization and until all cycles of apheresis are completed
8. Member does **NOT** have **ANY** of the following ("a" to "f"):
    a. A baseline white blood cell count (WBC) less than 3 x 10^9/L and/or a baseline platelet count less than 100 x10^9/L not related to hypersplenism
    b. Advanced liver disease defined as **ANY** of the following ("i" to "iv"):
        i. Persistent aspartate transaminase (AST), alanine transaminase (ALT), or direct bilirubin value greater than 3-times the upper limit of normal (ULN)
        ii. Baseline prothrombin time or partial thromboplastin time greater than 1.5-times the ULN
        iii. MRI of the liver demonstrating clear evidence of cirrhosis
        iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis.
    c. Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m^2
    d. Any prior or current malignancy (with the exception of adequately treated basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder
    e. Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary nonpolyposis colorectal cancer syndrome and familial adenomatous polyposis)
    f. Active infection, including uncontrolled HCV or HBV infection.
9. Member has **NOT** previously received gene therapy (including elivaldogene autotemcel) **OR** an allogeneic HSCT in their lifetime
10. Elivaldogene autotemcel will be administered at a Skysona Qualified Treatment Center (QTC)
11. The administration of elivaldogene autotemcel (Skysona) will not exceed one single dose as provided by the manufacturer

Approval duration: 12 months to allow for a one-time infusion of therapy

Elivaldogene autotemcel (Skysona) is considered **experimental or investigational** for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Elivaldogene autotemcel (Skysona) is indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD).
- Before mobilization, apheresis, and myeloablative conditioning are initiated, confirm that hematopoietic stem cell (HSC) transplantation is appropriate for the patient.
- Elivaldogene autotemcel (Skysona) is an autologous HSC-based gene therapy that is prepared from the patient's HSCs, which are collected via apheresis procedures. Patients must undergo HSC mobilization and apheresis to obtain CD34+ cells for manufacturing. Therefore, anti-retroviral medications should not be taken for at least one month prior to initiating medications for stem cell mobilization and for the expected duration for elimination of the medications, and until all cycles of apheresis are complete.
- Full myeloablative and lymphodepleting conditioning must be administered before infusion of elivaldogene autotemcel (Skysona).
- Dosing of elivaldogene autotemcel (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.
- Administration of elivaldogene autotemcel (Skysona) occurs at participating sites. Prior to administration, one must verify the patient's identity matches the unique patient identification information on the elivaldogene autotemcel (Skysona) infusion bag(s) prior to infusion. Do not use an in-line blood filter or an infusion pump to administer elivaldogene autotemcel (Skysona). Administer each infusion bag of elivaldogene autotemcel (Skysona) via intravenous infusion (drip) by gravity flow over a period of less than 60 minutes, and no more than 4 hours after thawing.

Dose Adjustments

- Hepatic Impairment – Elivaldogene autotemcel (Skysona) has not been studied in patients with hepatic impairment. Patients should be assessed for hepatic impairment to ensure HSC transplantation is appropriate.
- Renal Impairment - Elivaldogene autotemcel (Skysona) has not been studied in patients with renal impairment. Patients should be assessed for renal impairment, defined as creatinine clearance ≤ 70 mL/min/1.73 m^2, to ensure HSC transplantation is appropriate.

Drug Availability

- Elivaldogene autotemcel (Skysona) is a cell suspension for intravenous infusion.
- A single dose of elivaldogene autotemcel (Skysona) contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight, suspended in a solution containing 5% dimethyl sulfoxide (DMSO).
- Match the identity of the patient with the patient identifiers on the metal cassette(s), infusion bag(s), and Lot Information Sheet upon receipt.
- Elivaldogene autotemcel (Skysona) is composed of one or two infusion bags; each infusion bag contains approximately 20 mL.
- Keep the infusion bag(s) in the metal cassette(s) and store in the vapor phase of liquid nitrogen at less than or equal to -140°C (≤ -220°F) until ready for thaw and administration.
- Thaw elivaldogene autotemcel (Skysona) prior to infusion.
- Do not re-freeze after thawing.
- The product must not be altered or irradiated.

PRECAUTIONS:

Boxed Warning

- Hematologic malignancy, including life-threatening cases of myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients treated with elivaldogene autotemcel (Skysona). The cancers appear to be the result of the elivaldogene autotemcel (Skysona) lentiviral vector, Lenti-D, integration in proto-oncogenes. Monitor patients closely for evidence of malignancy through complete blood counts at least every 3 months and through assessments for evidence for clonal expansion or predominance at least twice in the first year and annually thereafter; consider bone marrow evaluations as clinically indicated.

Contraindications

- None

Precautions/Warnings

- **Serious Infections:** Life-threatening bacterial and viral infections may occur. Monitor patients for signs and symptoms of infection.
- **Prolonged Cytopenias:** Patients may exhibit cytopenias >1 year after treatment with elivaldogene autotemcel (Skysona). Monitor patients for bleeding and infection.
- **Delayed Platelet Engraftment:** Monitor patients for thrombocytopenia and bleeding until platelet engraftment and count recovery.
- **Risk of Neutrophil Engraftment Failure:** Monitor absolute neutrophil counts and if neutrophil engraftment does not occur, give rescue cells.

- **Hypersensitivity Reactions**: Allergic reactions may occur with the infusion of elivaldogene autotemcel (Skysona). The dimethyl sulfoxide (DMSO) in elivaldogene autotemcel (Skysona) may cause hypersensitivity reactions, including anaphylaxis.
- **Anti-retroviral Use:** Patients should not take prophylactic HIV anti-retroviral medications for at least one month prior to mobilization, or for the expected duration for elimination of the medications, and until all cycles of apheresis are completed. If a patient requires anti-retrovirals for HIV prophylaxis, then confirm a negative test for HIV before beginning mobilization and apheresis of CD34+ cells.
- **Interference with Serology Testing:** Patients who have received elivaldogene autotemcel (Skysona) are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a false-positive test for HIV. Therefore, patients who have received elivaldogene autotemcel (Skysona) should not be screened for HIV infection using a PCR-based assay.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J3387	Injection, elivaldogene autotemcel, per treatment

ICD-10 Diagnosis Codes That Support Medical Necessity

E71.520	Childhood cerebral X-linked adrenoleukodystrophy
E71.521	Adolescent X-linked adrenoleukodystrophy

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Cerebral adrenoleukodystrophy (CALD) - a rare X-linked genetic disorder caused by mutations in the ABCD1 gene resulting in a reduction in adrenoleukodystrophy protein (ALDP) and increase in very long-chain fatty acids (VLCFAs) that cause demyelination in the CNS and result in a progressive neurodegeneration.

Gene therapy - Gene therapies treat diseases by modifying or manipulating the expression of a gene or altering the properties of living cells for therapeutic use including: (1) replacing a disease-causing gene with a healthy copy of the gene, (2) inactivating a disease-causing gene that is not functioning properly, or (3) introducing a new or modified gene into the body to help treat a disease.

Loes score – used to assess the extent of lesions on MRI; scores range from 0 to 34, with higher scores indicating an increased extent of lesions on MRI.

Neurologic Function Scale - used to assess disease severity; scores range from 0 to 25, with higher scores indicating more severe deficits).

RELATED GUIDELINES:

None

OTHER:

Hearing/auditory processing problems	I
Aphasia/apraxia	I
Loss of communication	3
Vision impairment/fields cut	I
Cortical blindness	2
Swallowing difficulty or other central nervous system dysfunction	2
Tube feeding	2
Running difficulties/hyperreflexia	I
Walking difficulties/spasticity/spastic gait (no assistance)	I
Spastic gait (needs assistance)	2
Wheelchair required	2
No voluntary movement	3
Episodes of incontinence	I
Total incontinence	2
Nonfebrile seizures	I
Possible Total	25

Notes: The cALD Neurologic Function Scale is a demerit clinical scoring system used by various investigators to describe disease severity. Any non-zero score denotes clinically evident disease. Maximal disease within a domain scores the total of all grades within that domain (eg, a patient with "loss of communication" scores 5). Bolded items indicate "major functional disability" end points used by some investigators.

Abbreviation: cALD, cerebral adrenoleukodystrophy.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/09/25.

GUIDELINE UPDATE INFORMATION:

11/15/22	New Medical Coverage Guideline – Elivaldogene autotemcel (Skysona) for 4 to 17 year old, biological males with genetically confirmed early, active cerebral adrenoleukodystrophy (CALD) who are clinically stable and able to undergo a HSCT but do not have a HLA-matched family donor.
01/01/23	Revision: Approval duration changed from 3 months to 12 months.
05/15/23	Revision to guideline consisting of updating ICD-10 codes and references.
05/15/24	Revision to guideline consisting of revising the position statement to limit genetic testing results to laboratory documentation and updating references.
05/15/25	Review and revision to guideline consisting of revising the box warning to include acute myeloid leukemia,increasing the frequency of CBC monitoring to 3 months from 6 months, and updating the references.
01/01/26	Revision: Added HCPCS code J3387 and removed code J3590.