Skysona (elivaldogene autotemcel)

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Skysona (elivaldogene autotemcel) policy is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met, and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Skysona is indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD) without an available human leukocyte antigen (HLA)-matched donor for allogenic stem cell transplant. Early, active CALD 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 0.5-9.

This indication is 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 a confirmatory trial(s).

Limitations of Use:

- Skysona does not prevent the development of or treat adrenal insufficiency due to adrenoleukodystrophy.
- 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 human adenosine triphosphate binding cassette, sub family D, member 1 (ABCD1) gene.
- Skysona has not been studied in CALD secondary to head trauma.
- Given the risk of hematologic malignancy with Skysona, and unclear long-term durability of Skysona and human adrenoleukodystrophy protein (ALDP) expression, careful consideration should be given to the appropriateness and timing of treatment for each boy, especially for boys with isolated pyramidal tract disease based on available treatment options since their clinical manifestations do not usually occur until adulthood.

Skysona has a boxed warning regarding hematologic malignancy. Hematologic malignancy, including life-threatening cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), have occurred in patients treated with Skysona. The cancers appear to be linked to lentiviral vector, Lenti-D, integration

into 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.

Skysona also contains warnings for serious infections, prolonged cytopenias, delayed platelet engraftment, and risk of neutrophil engraftment failure, hypersensitivity reactions, anti-retroviral use, and laboratory test interference.

The safety and effectiveness of Skysona in pediatric patients less than 4 years of age has not been established.

POLICY

Required Documentation

Submission of the following information is necessary to initiate the prior authorization review:
Chart notes, medical records, or lab results documenting all of the following:

1. Mutation in the ABCD1 gene
2. Elevated very long chain fatty acids (VLCFA) values
3. Active central nervous system (CNS) disease on central radiographic review of brain magnetic resonance imaging (MRI) demonstrating:
    a. Loes score between 0.5 and 9 (inclusive) on the 34-point scale, and
    b. Gadolinium enhancement on MRI of demyelinating lesions
4. Neurologic Function Score (NFS) less than or equal to 1
5. Baseline hematologic, hepatic, renal, and cardiac assessments.

Prescriber Specialties

This medication must be prescribed by or in consultation with a neurologist or physician who specializes in the treatment of cerebral adrenoleukodystrophy (CALD).

Criteria for Initial Approval

Skysona (elivaldogene autotemcel) may be considered **medically necessary** and authorization of 3 months may be granted for one-time treatment for use in members with cerebral adrenoleukodystrophy (CALD) when ALL of the following criteria are met:

1. Member is 4 to 17 years of age at the time of infusion of elivaldogene autotemcel
2. Member has documented diagnosis of active cerebral X-linked adrenoleukodystrophy (CALD) as defined by ALL of the following:
    a. Confirmed mutation in the *ABCD1* gene
    b. Elevated very-long-chain fatty acids (VLCFAs) values per reference range of the laboratory performing the test
    c. Presence of active central nervous system (CNS) disease documented by:
        i. Loes score between 0.5 and 9 (inclusive) on the 34-point scale, AND
        ii. Gadolinium enhancement on MRI of demyelinating lesions
3. Documented neurologic function score (NFS) score ≤ 1 (see Appendix A)
4. Member is eligible for a hematopoetic stem cell transplant (HSCT) but is unable to find a human leukocyte antigen (HLA)-matched donor.
5. Member must have NONE of the following:
    a. History of receiving prior gene therapy or allogeneic hematopoietic stem cell transplant
    b. Peripheral blood absolute neutrophil count (ANC) < 1500 cells/cubic millimeter
    c. Platelet count < 100,000 cells/cubic millimeter
    d. Uncorrected bleeding disorder
    e. Hemoglobin < 10 g/dL
    f. Aspartate transaminase (AST) > 2.5 times the upper limit of normal (ULN)

g. Alanine transaminase (ALT) > 2.5 times the upper limit of normal (ULN)
h. Total bilirubin value > 3.0 mg/dL, except if member has also been diagnosed with Gilbert's Syndrome and member is otherwise stable
i. Left ventricular ejection fraction (LVEF) < 40%
j. Baseline estimated glomerular filtration rate (eGFR) < 70 ml/min/1.73m^2 OR actual or calculated creatinine clearance < 50 mL/min
k. Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to; hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome, and familial adenomatous polyposis)
l. Any clinically significant uncontrolled, active bacterial, viral, fungal, parasitic, or prion associated infection, including but not limited to; positive human immunodeficiency virus (HIV-1 or HIV-2), human T lymphotropic virus 1 (HTLV-1), active hepatitis B virus, and hepatitis C virus
m. Member will be monitored for evidence of malignancy per protocol outlined in the prescribing information following receipt of Skysona infusion.

Skysona (elivaldogene autotemcel) is considered **not medically necessary** for patients who do not meet the criteria set forth above.

Continuation of Therapy
Repeat treatment of Skysona for any indication is considered investigational, as the safety and efficacy beyond one dose has not been studied. The evidence is insufficient to determine the effects on net health outcomes.

Dosing and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The minimum recommended dose is 5.0 x 10^6 CD34+ cells per kg of body weight.

Quantity Limits
Skysona approvals will be limited to one treatment per lifetime.

Other Considerations
- Elivaldogene autotemcel was not studied in combination with statins, Lorenzo's Oil, or dietary regimens used to lower VLFCA levels. Prescriber's discretion in advised regarding the continuation of VLFCA lowering treatments after elivaldogene autotemcel administration.
- Where feasible, the individual's vaccination should be up to date with all age-appropriate vaccinations before elivaldogene autotemcel administration.
- Where feasible, the individual should receive periodical monitoring for hematological malignancies, including Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) .
- Final administration of elivaldogene autotemcel may be limited based on myeloablative and lymphodepleting conditioning requirements.

CLINICAL RATIONALE

Background
Cerebral adrenoleukodystrophy (CALD) is a genetic disorder caused by a mutation in the *ABCD1* gene. It is the childhood-onset form of ALD and leads to the accumulation of very-long-chain fatty acids in the brain and adrenal glands. This can cause damage to the myelin sheaths in the brain and spine which is required for normal functioning. CALD is an X-linked condition and as a result mainly affects males while females are often carriers with no or very mild symptoms (1).

Skysona (elivaldogene autotemcel) adds functional copies of the *ABCD1* cDNA into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with Lenti-D LVV. After Skysona infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes capable of production functional adrenoleukodystrophy protein (ALDP). Functional ALDP can then participate in the local degradation of very-long-chain fatty acids, which is believed to slow or possibly prevent inflammation and demyelination (2).

Efficacy

Skysona (elivaldogene autotemcel) was approved by the FDA after reviewing two 24-month, open-label, single-arm studies comparing confirmed CALD patients (patients with neurologic function score (NFS) of less than or equal to 1 and a Loes score between 0.5 and 9, showing limited or no neurologic changes) with an external natural history cohort that went untreated. Patients were diagnosed with early, active CALD with mutations in the ABCD1 gene, had gadolinium enhancement (GdE+) on MRI, and had elevated VLCFAs. ALD-102 was a Phase 2/3 study with 32 males ≤17 years of age looking at two primary endpoints: absence of major functional disability (MFD) at 24-months, and proportion of patients with acute or chronic graft-versus-host-disease (≥grade II) by month 24. To be included in the analysis, patients had to develop symptoms (NFS≥1) and then be followed for a minimum of 24 months after first symptom onset. Of the eleven elivaldogene autotemcel treated patients meeting these criteria, there was a 72% likelihood of MFD-free survival at 24-months, as compared to a 43% likelihood of MFD-free survival at 24-months in the untreated natural history cohort. The MFD-free survival met the FDA requirement for approval. The second study, ALD-104, was not completed at the time of approval and mimicked inclusion and exclusion criteria of ALD-102, but it is evaluating different primary endpoints: absence of MFD at month 24, and patients with neutrophil engraftment during the product infusion. Additionally, as a follow-up to the accelerated approval, the FDA is requiring the manufacturer to conduct continued monitoring of these patients for a period of 15 years due to safety concerns and to elicit additional efficacy data.

Only a small subset of patients have exceeded the 24 months of observation during the trial, but there is data to show durability for up to 7 years in some patients as researchers are continuing monitoring of outcomes. Without treatment, it is expected that patients diagnosed with CALD will develop continually advancing levels of disability and have a life expectancy to reach the second decade of life. Some of these patients have a preferred alternative treatment in hematopoietic stem cell transplant (HSCT). However, it is estimated that only 30% of these patients have a matched sibling donor where they would be eligible for HSTC.

Safety

During the aforementioned trials, there were several concerning safety-related events that the FDA determined outweighed by the efficacy in a patient population that has few, or no alternatives. Development of myelodysplastic syndrome after elivaldogene autotemcel infusion occurred in 3 patients resulting in a black boxed warning for hematologic malignancy and requires follow-up for at least 15 years post-infusion. The concern of hematologic malignancy results from integration of the lenti-D lentiviral vector into proto-oncogenes. It is unknown which proto-oncogenes will lead to malignancy, but 98% of patients treated with elivaldogene autotemcel in the clinical trials have integrations into MECOM (MDS1 and EVI1 complex locus protein EVI1—a protein that is encoded by the MECOM gene).

Additionally, the non-laboratory adverse reactions occurring at a rate ≥20% include; mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache, and rash. Laboratory abnormalities occurring at ≥40% included; leukopenia, lymphopenia, thrombocytopenia, neutropenia, anemia, and hypokalemia. The long-term follow-up study (LTF-304) will continue to monitor both safety and efficacy of Skysona, and final reports regarding ALD-102 and ALD-104 are expected in July 2032 and December 2038, respectively.

APPENDICIES

Appendix A: CALD Neurologic Function Score

Functional Assessment	Score
Hearing/auditory processing problems	1
Aphasia/apraxia	1
Loss of communication	3
Vision impairment/fields cut	1
Cortical blindness	2
Swallowing difficulty or other CNS dysfunction	2
Tube feeding	2
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Spastic gait (needs assistance)	2
Wheelchair required	2
No voluntary movement	3
Episodes of urinary or fecal incontinence	1
Total urinary or fecal incontinency	2
Nonfebrile seizures	1
Possible Total	25

Appendix B: Loes Score

MRI Brain Pattern	Score
Pari Petoccipital white matter	0-4
Temporal-anterior white matter	0-4
Frontal white matter Periventricular Central Subcortical Local atrophy	0-4
Corpus callosum Splenium Body Genu Splenius atrophy Genu Atrophy	0-5
Optical way	0-4
Auditory pathway	0-4
Projection fiber abnormalities	0-2
Cerebellum	0-2
Basal ganglia	0-1
Global atrophy	0-4
Total	**34**

Appendix C: Major Functional Disability

- Loss of communication
- Cortical blindness
- Requirement of tube feeding
- Total incontinence
- Wheelchair dependence
- Complete loss of voluntary movement

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J3387 – Injection, elivaldogene autotemcel, per treatment (effective 1/1/26)
- C9399 – Unclassified drugs or biologicals
- J3590 – Unclassified biologicals

REFERENCES

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POLICY HISTORY

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