elivaldogene autotemcel (Skysona®)

Policy # 00837
Original Effective Date: 06/12/2023
Current Effective Date: 06/12/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider elivaldogene autotemcel (Skysona®)‡ for the treatment of early, active cerebral adrenoleukodystrophy to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of elivaldogene autotemcel (Skysona) will be considered when all of the following criteria are met:

- Patient has a documented diagnosis of early, active cerebral adrenoleukodystrophy (CALD) as defined by:
  - Confirmed pathogenic variant in the *ABCD1* gene; AND
  - Elevated very long chain fatty acids (VLCFAs); AND
  - Presence of active central nervous system (CNS) disease documented by:
    - Loes score between 0.5 and 9 (inclusive) on the 34-point scale; AND
    - Gadolinium enhancement on magnetic resonance imaging (MRI) of demyelinating lesions; AND
- Patient is 4 to 17 years of age at the time of infusion of Skysona; AND
- Patient has a documented neurologic function score (NFS)≤1 (asymptomatic or mildly symptomatic); AND
- Patient is a candidate for allogeneic hematopoietic cell transplantation, but ineligible due to the absence of a human leukocyte antigen-identical or human leukocyte antigen-matched donor; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

elivaldogene autotemcel (Skysona®)

Policy # 00837
Original Effective Date: 06/12/2023
Current Effective Date: 06/12/2023

- Patient does NOT have:
  - History of receiving prior gene therapy or allogeneic hematopoietic stem cell transplant; OR
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Hematological compromise as evidenced by ANY of the following:
    - Peripheral blood absolute neutrophil count (ANC) <1500 cells/mm^3; OR
    - Platelet count < 100,000 cells/mm^3 OR
    - Hemoglobin <10 g/dL; OR
    - Uncorrected bleeding disorder; OR

    *(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Hepatic compromise as evidenced by ANY of the following:
    - Liver cirrhosis or bridging fibrosis based on MRI or liver biopsy; OR
    - AST > 2.5 times the upper limit of normal; OR
    - ALT >2.5 times the upper limit of normal; OR
    - Total bilirubin value >3.0 mg/dL, except if there is a diagnosis of Gilbert's syndrome and the participant is otherwise stable; OR

    *(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Cardiac compromise as evidenced by a left ventricular ejection fraction (LVEF) <40%; OR
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Renal compromise as evidenced by a baseline eGFR <70 mL/min/1.73 m^2 OR actual or calculated CrCl <50 mL/min; OR
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (e.g., hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome, familial adenomatous polyposis); OR
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

  - Any clinically significant uncontrolled, active bacterial, viral, fungal, parasitic, or prion associated infection; OR
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Any condition(s) that would contraindicate continued MRI Studies; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient will not receive more than one dose of Skysona per lifetime.
- Patient will receive elivaldogene autotemcel at a Skysona Qualified Treatment Center (QTC).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of elivaldogene autotemcel (Skysona) when the patient has an HLA-identical or HLA-matched donor or has received prior gene therapy or hematopoietic stem cell transplant to be **not medically necessary.****

Based on review of available data, the Company considers the use of elivaldogene autotemcel (Skysona) when the patient has evidence of hematological compromise, hepatic compromise, cardiac compromise, or renal compromise to be **not medically necessary.****

Based on review of available data, the Company considers the use of elivaldogene autotemcel (Skysona) in patients with any immediate family member with a known familial cancer syndrome, any clinically significant uncontrolled infection, or any condition that would be a contraindication for continued MRI studies to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of elivaldogene autotemcel (Skysona) when patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

elivaldogene autotemcel (Skysona®)

Policy # 00837
Original Effective Date: 06/12/2023
Current Effective Date: 06/12/2023

Policy Guidelines

Qualified Treatment Centers
https://www.skysona.com/find-a-qualified-treatment-center

Background/Overview

Skysona is a gene therapy indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy. It works by adding functional copies of the *ABCD1* cDNA into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with a Lenti-D lentiviral vector (LVV). After Skysona infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes capable of producing functional adrenoleukodystrophy protein (ALDP). Functional ALDP can then participate in the local degradation of very-long-chain fatty acids (VLCFAs), which is believed to slow or possibly prevent further inflammation and demyelination.

Full myeloablative conditioning must be administered before infusion of Skysona. The administration and preparation processes are complex and require hospitalization. The main steps involved include:

- Mobilization and apheresis (approximately 1 week)
- Cells sent to manufacturing site for production (approximately 51-65 days)
- Myeloablative conditioning with busulfan and lymphodepletion with cyclophosphamide and fludarabine
- Drug product administration via IV infusion
- Hospitalization for approximately 2 months after infusion.

Skysona carries a boxed warning regarding hematologic malignancy due to patients being diagnosed with myelodysplastic syndrome between 14 months and 7.5 years after Skysona administration. The three instances documented at the time of product approval were found to be the result of Skysona Lenti-D lentiviral vector integration into proto-oncogenes. Patients who receive Skysona should be monitored lifelong for hematologic malignancy.

Cerebral Adrenoleukodsytrophy (CALD) is one of the adrenoleukodystrophies caused by a mutation in the *ABCD1* gene on the X chromosome resulting in accumulation of very-long-chain-fatty acids

(VLCFAs) which lead to neurodegeneration. Because the condition is X-linked, CALD primarily affects males. Approximately 40 boys are diagnosed with CALD in the United States each year. Boys with CALD typically present with neurologic symptoms between 3 and 10 years of age. After an initial period of normal development, symptoms typically include behavioral problems and learning disabilities. Progressive symptoms include diminished visual acuity, hearing loss, gait instability, weakness and stiffness of limbs, and seizures. Within 2-3 years, symptoms progress to a loss of most neurologic function and total disability, with death occurring by the second decade of life.

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for early-stage CALD. Observational studies have reported 5- and 8- year survival rates of 56%, with 5-year survival rates as high as 92% among patients treated at very early stages of the illness. It is estimated that only about 30% of patients with CALD are able to find a matched sibling donor. No other disease-modifying treatments exist for CALD. Symptomatic and supportive treatments include physical therapy, psychological support, and special education.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Skysona was approved in September 2022 under the accelerated approval pathway to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD)

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The safety and efficacy of Skysona were assessed in two 24-month, open-label, single-arm studies in patients with early, active CALD as defined by Loes score between 0.5 and 9 (inclusive) and gadolinium enhancement (GdE+) on MRI, as well as neurologic function score (NFS) of $\leq$1, indicating limited changes in neurologic function. The NFS was used to evaluate 15 domains of

neurological function with a maximum score of 25. A total NFS=0 indicates absence of neurologic dysfunction or asymptomatic disease. The patients enrolled and treated with Skysona (Study 1, n=32; Study 2, n=25) all had elevated very long chain fatty acid (VLCFA) levels and confirmed mutations in the *ABCD1* gene. The efficacy of Skysona was compared to an external untreated natural history control. Data for the natural history population in the retrospective natural history study was collected from existing medical records for patients with CALD. The natural history population had early, active disease at diagnosis, though gadolinium status was defined by either having a GdE+ MRI during the study or unknown GdE status and clinical course that suggested active disease.

Skysona Studies

Patients in both studies underwent mobilization and apheresis to allow for cell collection followed by pre-treatment myeloablative conditioning and lymphodepletion before receiving Skysona. The agents used for mobilization and apheresis and lymphodepletion varied slightly between studies. After Skysona administration, G-CSF was administered to the majority of patients (75% in Study 1 and 100% in Study 2) beginning on Day 5.

Comparison of Skysona with the Natural History of CALD

A post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms to time to first Major Functional Disability (MFD) or death in Skysona treated and Natural History patients. The MFDs are defined as loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement. To be included in the analysis, patients had to have symptoms at baseline or be asymptomatic at baseline and have developed symptoms during the course of follow-up in the study. Additionally, they had to have at least 24 months of follow-up after initial NFS $\geq$1 or have had an event (MFD or death).

Slower progression to MFD or death from time of symptom onset (first NFS $\geq$1) was seen for early, active CALD patients treated with Skysona compared to a similar natural history of disease. Kaplan-Meier (KM) estimated MFD-free survival at Month 24 from time of first NFS $\geq$1 were 72% (95% CI: 35%, 90%) for the symptomatic Skysona subpopulation and 43% (95% CI: 10%, 73%) for the natural history population. There were insufficient data beyond 24 months for the symptomatic Skysona subpopulation to assess long-term MFD-free survival as compared to the natural history of disease. There was insufficient duration of follow-up to assess efficacy in Skysona treated patients who remained asymptomatic.

elivaldogene autotemcel (Skysona®)

Policy # 00837
Original Effective Date: 06/12/2023
Current Effective Date: 06/12/2023

Comparison of Skysona with Allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT)
There were insufficient data to compare relative efficacy of Skysona to the standard of care, allogeneic hematopoietic stem cell transplant (allo-HSCT) in the treatment of CALD. However, while it does not inform the efficacy analysis, comparison of Skysona with an external allo-HSCT control (pooled from Study 3 and from a mixed prospective and retrospective allo-HSCT data collection study, Study 4) was performed for overall survival due to concerns about treatment-related toxicities. Overall survival was analyzed as time-to-event Kaplan Meier estimates comparing Skysona to early, active allo-HSCT subpopulations by donor type: human leukocyte antigen (HLA)-Matched allo-HSCT Subpopulation (n=34) and HLA-Mismatched allo-HSCT subpopulation (n=17). There were insufficient long-term data to compare overall survival beyond Month 24. However, a distinct difference in overall survival in the first 9 months following treatment was seen for the subpopulation who received allo-HSCT from an HLA-mismatched donor as compared to Skysona and allo-HSCT from an HLA-matched donor. While this analysis does not provide evidence of efficacy of Skysona, it does demonstrate a survival advantage of Skysona as compared to allo-HSCT from an HLA-mismatched donor, with early mortality in the HLA-mismatched allo-HSCT subpopulation largely attributed to allo-HSCT-related toxicities.

References

1. Skysona [package insert]. Bluebird Bio, Inc. Somerville, MA. Updated September 2022.
2. Skysona (elivaldogene autotemcel) New Drug Review. IPD Analytics. Updated October 2022.

Policy History

Original Effective Date: 06/12/2023
Current Effective Date: 06/12/2023
05/04/2023 Medical Policy Committee review
05/10/2023 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 05/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

elivaldogene autotemcel (Skysona®)

Policy # 00837
Original Effective Date: 06/12/2023
Current Effective Date: 06/12/2023

descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3490, J3590, C9399
ICD-10 Diagnosis	E71.520, E71.521

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company

recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.