Skysona (elivaldogene autotemcel)
Clinical Coverage Criteria

Description

Skysona (elivaldogene autotemcel) is an autologous hematopoietic stem cell (HSC)-based gene therapy, indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD).

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).

Policy

This Policy applies to the following Fallon Health products:

☒ Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)

☒ MassHealth ACO

☒ NaviCare HMO SNP, NaviCare SCO

☒ PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)

☒ Community Care

Skysona (elivaldogene autotemcel) requires prior authorization by a Fallon Health Medical Director.

Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)
Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Medicare statutes and regulations do not have coverage criteria for Skysona (elivaldogene autotemcel). Medicare does not have an NCD for Skysona (elivaldogene autotemcel). National Government Services, Inc. is the Medicare Administrative Contractor (MAC) with jurisdiction over Part A and B services in Fallon Health's service area. National Government Services, Inc. does not have an LCD for Skysona (elivaldogene autotemcel) (Medicare Coverage Database search 01/04/2024).

Coverage criteria for Skysona (elivaldogene autotemcel) are not fully established by Medicare, therefore, the Plan's clinical coverage criteria are applicable.

MassHealth ACO
Fallon Health follows Medical Necessity Guidelines/coverage criteria published by MassHealth when making medical necessity determinations for MassHealth members.

MassHealth has coverage criteria for Skysona (elivaldogene autotemcel) effective 12/4/2023:

MassHealth Drug List: **Skysona**.

NaviCare HMO SNP, NaviCare SCO
For plan members enrolled in NaviCare, Fallon Health first follows guidance from CMS when making medical necessity determinations. CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) and applicable Medicare statutes and regulations are the basis for medical necessity determinations.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health will then follow Medical Necessity Guidelines/coverage criteria published by MassHealth when making necessity determinations for NaviCare members.

PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Fallon Health Clinical Coverage Criteria

Skysona (elivaldogene autotemcel) is considered medically necessary to slow the progression of neurologic dysfunction in plan members with early, active cerebral adrenoleukodystrophy (CALD) who meet all of the following coverage criteria:

1. Age ≥ 4 years and ≤ 17 years at the time of treatment.

2. Diagnosis of adrenoleukodystrophy confirmed by both:
   a. Elevated plasma very long chain fatty acids (VLCFA) values according to the standard reference values of the performing laboratory, and
   b. The presence of a pathogenic variant in the adenosine triphosphate binding cassette, sub family D member 1 (ABCD1) gene detected by genetic testing.

3. Documentation of early, active CALD as defined by all of the following:
   a. Active CNS disease established by central radiographic review of brain magnetic resonance imaging (MRI) demonstrating:
      i. Loes score between 0.5 and 9 (inclusive) on the 34-point scale, and
      ii. Gadolinium enhancement on MRI of demyelinating lesions.
   b. Neurologic Function Score (NFS) ≤ 1.

4. The ordering/treating physician is a neurologist with specialized training in the treatment of CALD and Skysona will be administered at a Skysona Qualified Treatment Center.

5. A transplant specialist has evaluated the member and attests that the member is clinically stable and eligible to undergo a hematopoietic stem cell transplant (HSCT), however, an HLA-matched sibling donor (excluding female heterozygotes) is unavailable.

Exclusions

- Retreatment with Skysona or use after failure of allogeneic hematopoietic stem cell transplant (HSCT).
- The safety and efficacy of Skysona in children less than 4 years of age have not been established.
- Use to treat or prevent adrenal insufficieny.

- Use in patients with CALD secondary to head trauma.
- There are no available data for Skysona administration in a geriatric population nor is it expected or intended to be used in this population.
- Skysona does not prevent the development of or treat adrenal insufficiency due to adrenoleukodystrophy.

Summary of Evidence

Background

Adrenoleukodystrophy (ALD) is a rare X-linked inborn error of metabolism caused by mutations in the adenosine triphosphate binding cassette, sub family D member 1 (ABCD1) gene (Zhu et al., 2020). Mutations in the ABCD1 gene prevent the production of the adrenoleukodystrophy protein (ALDP) in about 75% of people with this disorder. ALDP is located in the membranes of cell structures called peroxisomes. ALDP brings a group of fats called very long-chain fatty acids (VLCFAs) into peroxisomes, where they are broken down. With little or no functional ALDP, VLCFAs are not broken down and they build up in the body (NLM, 2013).

In males suspected of having ALD, the measurement of very long chain fatty acids (VCLFA) in blood is diagnostic, with nearly 100% sensitivity. However, this diagnostic marker can be normal in 15-20% of women (Huffnagel et al., 2019). Genetic testing should be performed to confirm the diagnosis of ALD. After genetic confirmation in the proband, targeted testing for the identified mutation in immediate and extended family members should be offered to those at risk of developing ALD. To date, over 900 unique disease-causing mutations have been catalogued with no correlation to phenotypes, and there is no identified means of determining which males with ALD will develop which clinical features of the disorder. Furthermore, all clinical phenotypes of X-linked ALD can occur within the same nuclear family (Zhu et al., 2020).

In affected males, the clinical spectrum ranges from isolated adrenal insufficiency and slowly progressive myelopathy to devastating cerebral unflammatory demyelination, termed cerebral ALD (CALD). As ALD is an X-linked disease, females were previously considered asymptomatic carriers. It is now known that even though adrenal insufficiency and CALD rarely occurs in females (less than 1%), more than half will develop signs and symptoms of progressive myelopathy with the frequency increasing sharply with age (from 18% in women <40 years to 88% in women >60 years of age) (Engelen et al., 2014).

CALD presents in males between 4 and 12 years of age, with a peak age at onset of around 7 years, affecting approximately one-third of boys with X-linked ALD. CALD is rare after 15 years of age and almost never occurs before 2 years of age. Early on, the disease is a purely radiographic finding, as lesions on brain MRI far precede clinical manifestations. Brain MRIs should be obtained annually starting at 12 months of age and obtained more frequently every 6 months from the ages of 3–10 years, when the risk of developing cerebral CALD is highest. Affected boys subsequently develop learning and behavior problems. This first stage is followed by neurologic deterioration that includes increasing cognitive and behavioral abnormalities, cortical blindness, central deafness, and the development of quadriparesis. Very rarely, visual function is relatively preserved despite advanced central nervous system involvement. Approximately 20% of affected boys have seizures, which may be the first manifestation. Although the rate of deterioration can be variable, rapid progression is common, with total disability developing by 6 months to 2 years and death within 5 to 10 years of diagnosis (Zhu et al., 2020).

As elevations in VLCFA were recognized to be present at birth, the potential to use newborn screening for ALD was appreciated (Gupta et al., 2022). As survival and clinical outcomes are superior if treatment is offered in the early stages of cerebral ALD, ALD was nominated to be added to the U.S. Recommended Uniform Screening Panel in 2012 (Zhu et al., 2020). Newborn screening is a state-based public health program in the United States. This means that each state or territory has its own newborn screening program. Also, state or territory level policies govern which conditions are included in their newborn screening program. Massachusetts and many other states conduct newborn screening for X-linked ALD (HRSA Newborn Screening, 2023). As

newborn screening for ALD continues to expand in the United States, the reporting of mutations to variant databases and follow-up classification of variants based on phenotypic outcomes in affected families will be crucial to understanding the pathogenicity of new variants (Zhu et al., 2020).

Allogeneic hematopoietic stem cell transplant (allo-HSCT) has been the standard of care for the treatment of CALD since 2001. Retrospective studies have documented more favorable neurologic outcomes when allo-HSCT is performed early in the course of disease, prior to onset of significant neurologic dysfunction or radiographic disease burden. It has also been observed that allo-HSCT may increase rapidity of disease progression in patients with advanced cerebral disease (Loes score >9), and is no longer recommended for patients who meet this criterion. As such, allo-HSCT is performed in the early, active radiographic course of disease (Loes score 0.5-9 with gadolinium enhancement on brain MRI), which often corresponds to a time when patients are asymptomatic or mildly symptomatic (NFS 0 or 1).[1] The goal of treatment in this early, active phase of disease is to treat prior to the onset of significant neurologic dysfunction in an effort to prevent progression to disability and death, which is often rapid and more difficult to stabilize once disease is symptomatic.

In addition to the lack of efficacy in advanced disease, allo-HSCT does not reverse neurologic findings present at the time of transsplantation and does not stabilize cerebral disease for 3 to 24 months after stem cell infusion. Symptoms can progress during this time. This makes the early identification of potential allo-HSCT candidates essential. Transplant is ineffective for the adrenal manifestations of disease and is not felt to impact the development of adult onset adrenomyeloneuropathy. Transplantation requires the identification of a stem cell donor. If an acceptable human leukocyte antigen (HLA)-matched related donor is not available, then an unrelated donor or cord blood unit must be found. This process can take weeks and, in some circumstances, an acceptable unrelated stem cell donor may not be identified. Allo-HSCT comes with risks of acute mortality (~10% at day 100 from transplant) and late complications, a 5% risk failure of donor cell engraftment, and graft-versus-host disease (GVHD) (10–40% risk of acute GVHD and 20% risk of chronic GVHD). Patients with CALD must also meet institutional criteria for organ functioning, infectious disease status, and performance status. In summary, allo-HSCT is an effective therapy for patients who have early stage cerebral CALD, but it comes with significant short- and long-term risk (Zhu et al., 2020).

Transplantation of autologous, genetically modified hematopoietic stem cells (HSCs) is being extensively explored as an alternative to allo-HSCT for several conditions worldwide, with a large number of trials opened and patients being treated in the United States and Europe. This treatment strategy allows prompt identification of a stem cell source for transplant in every patient and overcomes the most severe immunological limitation of allo-HSCT represented by GVHD. In this setting, gene transfer is used to deliver a normal copy of the disease-causing gene (generally as cDNA) to the HSCs, thereby correcting their genetic defect (Shahryari et al., 2019).

[1] The CALD–specific neurologic function scale (NFS) and the Loes MRI severity score are used to help determine the suitability of a patient for transplant. The NFS is a 25-point, ALD-specific tool that assesses the severity of neurologic dysfunction by assigning scores to 15 different disabilities. Lower scores indicate fewer symptoms and higher scores indicate a more significant disability. The NFS score can be used to guide the recommendation for allo-HSCT, but there is no score that absolutely determines the decision for allo-HSCT. The Loes MRI severity score is a 34-point scale that assigns a score to an MRI based on the extent of white matter lesions, with higher scores indicating more significant ALD involvement (Loes et al., 2003).

MRI gadolinium contrast enhancement is used to indicate the presence of the inflammatory process, and there is an association between the presence of contrast enhancement on T1-weighted MRI and cerebral ALD progression. To be considered for allo-HSCT, patients must have evidence of cerebral disease on brain MRI with the presence of gadolinium contrast enhancement around a consistent lesion, indicating a minimum Loes MRI score of 1. The upper limit of the Loes MRI score is debated and often depends on the clinical scenario (Melhem et al., 2000).

Childhood CALD is one of the first neurologic disorders treated by the autologous gene therapy approach. Promising results reported in 2009 by Cartier and colleagues were obtained in 2 patients treated in the first clinical trial of HSC gene therapy for CALD using autologous CD34+ HSCs, transduced ex-vivo with Lenti-D lentiviral vector (also called elivaldogene autotemcel or eli-cel). Similar to what has been observed following allogeneic HSCT, clinical and neuroradiological disease stabilization was observed in the 2 boys, who had progressive demyelination but no HLA-matched or cord blood donors (Cartier et al., 2009). After these encouraging results, a larger, multicenter phase II/III clinical trial was launched in 2013 (ClinicalTrials.gov NCT01896102). Eligibility was restricted to patients who had gadolinium enhancement on MRI due to CALD and had the following signs of early-stage disease: 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 a Loes score (which ranges from 0 to 34, with higher scores indicating an increased extent of lesions on MRI) of 0.5 to 9.0. Patients who had an HLA-matched sibling who could donate cells for transplantation were excluded from the study. CD34+ cells that were obtained from the enrolled patients by means of apheresis were transduced with the Lenti-D lentiviral vector. Interim results for 17 patients who were between 4 and 13 years of age at the time of enrollment were published by Eichler et al. (2017). At baseline, the median Loes score was 2.0 (range, 1.0 to 7.5), and all the patients had a score of 0 on the neurologic function scale. Data on the interim safety and efficacy assessments were available as of April 2017. At the time of the interim analysis, 15 of the 17 patients (88%) were alive and free of major functional disabilities; these 15 patients maintained a score on the neurologic function scale of 0 or 1. Two patients had neurologic disease progression. One of these patients (Patient 2016) withdrew from the study and later died from complications of allogeneic transplantation. In the other patient (Patient 2018), neurologic function deteriorated rapidly after treatment; a major functional disability (total incontinence) developed by month 9, and additional major functional disabilities continued to develop, including cortical blindness, loss of communication, and wheelchair dependence. Approximately 22 months after the infusion, the patient died from a viral infection complicated by rhabdomyolysis and acute kidney and liver failure; these complications and the immediate cause of death were judged to be not directly related to the investigational therapy. Mean follow-up was 29.4 months (range, 21.6 to 42.0). This study has since met its target accrual of 32 subjects and has been closed to additional accruals. It in the data analysis stage, with the most recent results reported in abstract form (Yengi et al., 2019). A phase III trial was opened in January 2019 (NCT03852498) and 35 patients are enrolled. The estimated competion date is February 2024.

On October 18, 2021, bluebird bio, Inc. submitted a Biologics License Application to the FDA for licensure of elivaldogene autotemcel (eli-cel) with the proprietary name of Skysona. Bluebird bio, Inc. proposed the indication, “for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy (CALD) who do not have an available and willing human leukocyte antigen (HLA)-matched sibling hematopoietic stem cell (HSC) donor.” Results from two studies ALD-102 (NCT 01896102) and ALD-104 (NCT03852498) were submitted. Studies ALD-102 and ALD-104 enrolled subjects ages 4-17 years of age with early, active CALD, defined by a Neurologic Function Score (NFS) ≤1 and brain magnetic resonance imaging (MRI) with gadolinium enhancement (GdE+) and a Loes Score 0.5-9. Patients who had an HLA-matched sibling who could donate cells for transplantation were excluded from the studies.

The prespecified primary efficacy endpoint in ALD-102 was the percentage of subjects who had none of the 6 major functional disabilities (MFDs), were alive, did not receive a rescue allo-HSCT or rescue cell administration, and had not withdrawn or been lost to follow-up at Month 24 (i.e., Month 24 MFD-free survival). The 6 MFDs consisted of loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, complete loss of voluntary movement. Month 24 MFD-Free survival criteria was defined as: alive at 24 months post-infusion; had not developed any of the MFDs by 24 months post-infusion; had not received rescue cell administration or allo-HSCT by 24 months post-infusion; and had not withdrawn from the study or

had not been lost to follow-up by 24 months post-infusion. Percentage of participants who were alive and have none of the 6 major functional disabilities (MFDs) at Month 24 were reported.

As none of the study subjects in ALD-104 had reached 24 months of follow-up after treatment with Skysona at the time of BLA submission, so only the 32 ALD-102 subjects were evaluated for the primary efficacy endpoint. The study success criterion was superiority compared to a clinical benchmark of 50%. This benchmark was derived from 2 subpopulations from Study ALD-101 (a historical, retrospective study that included untreated CALD subjects). The 50% benchmark was chosen to demonstrate that Skysona was better than no treatment on MFD-free survival at 24 months. Twenty-three out of 26 (88%) subjects achieved Month 24 MFD-free survival (95% CI: 70%, 98%). ALD-102 was thus successful on the primary efficacy endpoint.

Athough ALD-102 met the success criterion for the primary efficacy endpoint, the FDA reviewers had concerns about the results. The main challenges were that few events (MFDs and deaths) occurred in the allo-HSCT and Skysona populations, and subjects treated with allo-HSCT and Skysona were generally diagnosed and treated at very early stages of disease. In comparison, event rates were high in the untreated natural history population, but the natural history population was older, with more advanced cerebral disease on MRI, and more likely to present with symptomatic disease at time of diagnosis or shortly after diagnosis. As a result, it was difficult to determine if the lower numbers of MFDs and deaths in the treated populations were due to a treatment effect or due to treatment at an early stage of disease with insufficient duration of follow-up to detect progression to MFD or death. It is unclear what the clinical course would have been in subjects with very early stages of disease had they not been treated. The reviewers conducted additional analyses to assess the clinical benefit.

In an analysis of MFD-free survival at 24 months, the reveiwers conducted a Kaplan-Meier (KM) time-to-event analysis that compared estimated time to progression to MFD or death from first NFS ≥ 1 among the untreated and treated subpopulations. The KM curves showed a striking difference between treatment groups (Skysona, allo-HSCT) and untreated natural history group. MFD-free survival KM estimates at the 24-month time point were 43% (95% CI: 10%, 73%), 69% (95% CI: 41%, 86%), and 72% (95% CI: 35%, 90%) for the untreated, allo-HSCT treated and Skysona-treated symptomatic subpopulations, respectively. It is notable that 28% of Skysona-treated symptomatic subjects experienced an MFD or death within 24 months of first NFS ≥ 1, as compared to 57% of the untreated natural history subpopulation. In essence, twice as many symptomatic natural history subjects progressed to MFD or death within 24 months of symptom onset as compared to a similar SKYSONA subpopulation.

The analysis of MFD-free survival at 24 months following first NFS ≥ 1 establishes an effect of Skysona on an intermediate clinical endpoint that is reasonably likely to predict long-term clinical benefit on MFD-free survival and slowing of progression of neurologic dysfunction as compared to the natural history of disease in symptomatic subpopulations. Success on this intermediate clinical endpoint forms the basis of accelerated approval, and confirmatory post-marketing review (PMR) studies will be required to assess long-term efficacy.

The primary evidence of efficacy lies in the outcomes of patients with parieto-occipital disease, as this pattern was the most common across studies, presents the earliest (in childhood) and is one of the most rapidly progressive if left untreated. Although numbers of subjects are small, there is evidence for efficacy in frontal patterns of disease, as well.

There are two populations for whom there is greater uncertainty regarding a favorable benefit-risk determination given the uncertainty of durability of effect and the magnitude of hematologic malignancy risk. Specifically, boys with isolated pyramidal tract pattern of disease on brain MRI and asymptomatic boys with very early radiographic findings (i.e., Loes score 1-2). Boys with the isolated pyramidal tract MRI pattern are known to have a slower progression of radiographic and clinical disease, typically with stable Loes score over time and prolonged duration between radiographic diagnosis and the onset of symptomatic disease (usually adulthood). Boys with very

early radiographic and asymptomatic disease are poorly represented in the natural history of disease due to frequent delayed diagnosis at the time the natural history subjects were diagnosed, and thus the time course of expected clinical progression of disease is relatively unknown. Therefore, relative long-term efficacy and benefit-risk assessment in these populations with isolated pyramidal tract disease or very early radiographic and asymptomatic disease could only be determined with a longer duration of follow-up.

The prespecified primary safety endpoint was proportion of participants who had experienced either acute ([>or=] grade ii) or chronic graft versus host disease (GVHD) by month 24. Acute GVHD graded on the Acute GVHD Grading Scale (I-IV): Grade I is characterized as mild disease, Grade II as moderate, Grade III as severe (involvement of any organ system), and Grade IV as life-threatening; chronic GVHD was determined by the Investigator. Percentage of participants who experienced with either acute (>= Grade II) or chronic GVHD at Month 24 were reported. The safety population included 67 subjects treated in the Phase 3 studies, ALD-102 and ALD-104.

Subjects were followed for a median of 23.5 months (range 1.4 months to 7.3 years). Safety data with a data cutoff of Aug. 18, 2021, were systematically reviewed, and cases of concern for malignancy or diagnosed malignancy that occurred at any time after the data cutoff date were reviewed on an ad hoc basis.

Insertional oncogenesis is the major safety concern with Skysona. Insertional oncogenesis is the primary safety concern with lentiviral vectors (LVVs). Insertional oncogenesis is the consequence of permanent alteration of the host genome by the vector. LVV integration into the DNA of target cells has the potential to affect the expression of nearby genes and may provide those cells with a growth advantage. Cells with a growth advantage may undergo preferential expansion and transform into a hematologic malignancy. At the time of FDA approval, three subjects had been diagnosed with hematologic malignancy (myelodysplastic syndromes, MDS). MDS is a rare hematologic malignancy in pediatric patients with no predisposition to development in children with CALD. However, it has been diagnosed in three subjects after treatment with Skyson. For all three subjects, the malignancy appears to have been caused by integration of the lentiviral vector into a proto-oncogene. In addition to the three subjects with MDS, the clinical review team has a specific concern for the possible development of malignancy in at least nine other subjects.

Two subjects died after treatment with Skysona. One underwent allo-HSCT due to CALD progression and subsequently died from HSCT complications. The second subject died from multisystem organ failure that was a complication of an adenovirus infection. He also had rapid progression of his CALD. It cannot be ruled out with certainty that his treatment with Slysona less than two years earlier may have contributed to the florid adenovirus infection.

There were many serious adverse reactions in the trials, having occurred in in 57% of subjects. The most common non-laboratory, non-cancer serious adverse reactions (≥ 3% incidence) that occurred after treatment with Skysona were febrile neutropenia (18%), pyrexia (18%), seizure (7%), pseudomonal bacteremia (3%), pancytopenia (3%), vascular device infection (3%), mucositis (3%), and vomiting (3%). No subjects were diagnosed with graft versus host disease.

Analysis of Evidence (Rationale for Determination)

The recommendation for accelerated approval is based primarily on the Kaplan-Meyer time to event analysis in a symptomatic subset of Skysona-treated subjects and similar untreated controls. Skysona slowed the progression of neurologic dysfunction (NFS ≥ 1) assessed by major functional disabilities (MFDs) or death at 24 months from time of symptom onset compared to an untreated natural history population. Confirmatory post-marketing review (PMR) studies will be required to assess long-term efficacy.

References

1. National Library of Medicine (NLM). Medline Plus. ABCD1 Gene. Last updated July 1, 2013. Available at: https://medlineplus.gov/genetics/gene/abcd1/. Accessed 07/24/2023.
2. Gupta AO, Raymond G, Pierpont EI, et al. Treatment of cerebral adrenoleukodystrophy: allogeneic transplantation and lentiviral gene therapy. *Expert Opin Biol Ther*. 2022 Sep;22(9):1151-1162.
3. Huffnagel IC, Dijkgraaf MGW, Janssens GE, et al. Disease progression in women with X-linked adrenoleukodystrophy is slow. *Orphanet J Rare Dis*. 2019 Feb 7;14(1):30.
4. Engelen M, Barbier M, Dijkstra IM, et al. X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. *Brain*. 2014 Mar;137(Pt 3):693-706
5. Moser AB, Jones RO, Hubbard WC, et al. Newborn Screening for X-Linked Adrenoleukodystrophy. *Int J Neonatal Screen*. 2016 Dec;2(4):15.
6. Health Resources & Services Administration (HRSA). Newborn Screening in Your State. Date Last Reviewed: June 2023. Available at: https://newbornscreening.hrsa.gov/your-state. Accessed July 24, 2023.
7. Zhu J, Eichler F, Biffi A, Duncan CN, Williams DA, Majzoub JA. The Changing Face of Adrenoleukodystrophy. *Endocr Rev*. 2020 Aug 1;41(4):577–9.
8. Mahmood A, Raymond GV, Dubey P, et al.. Survival analysis of haematopoietic cell transplantation for childhoodcerebral X-linked adrenoleukodystrophy: a comparison study. *Lancet Neurol.* 2007;6(8):687–692.
9. Loes DJ, Fatemi A, Melhem ER, et al.. Analysis of MRI patterns aids prediction of progression in X-linkedadrenoleukodystrophy. *Neurology*. 2003;61(3):369–374.
10. Melhem ER, Loes DJ, Georgiades CS, et al. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging inpredicting disease progression. *AJNR Am J Neuroradiol*. 2000; 21(5):839–844.
11. Orchard PJ, Blazar BR, Wagner J, et al.. Hematopoietic cell therapy for metabolic disease. *J Pediatr.* 2007;151(4):340–436.
12. Peters C, Charnas LR, Tan Y, et al.. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic celltransplantation experience from 1982 to 1999. *Blood.* 2004;104(3):881–888.
13. Raymond GV, Aubourg P, Paker A, et al.. Survival and functional outcomes in boys with cerebral adrenoleukodystrophywith and without hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2019;25(3):538–548.
14. Shahryari A, Saghaeian Jazi M, Mohammadi S, et al. Development and clinical translation of approved gene therapyproducts for geneticdisorders. *Front Genet*. 2019; 10:868.
15. Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al.. Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. *Science.* 2009;326(5954):818–823.
16. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. *NEngl J Med*. 2017; 377(17):1630–1638.
17. Yengi L, Parsons G, Pasackow E, et al.. Evidence that prevalent SMG6 insertions are not associated with abnormalclinical findings in patients treated with lenti-D autologous hematopoietic stem cell gene therapy for cerebraladrenoleukodystrophy. Paper presented at: Program of the 27th Annual Congress of the European Society for Gene and CellTherapy; 2019; Barcelona, Spain, 164. (Abstract P264).

Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage or reimbursement.

At this time, no product-specific ICD-10-PCS, CPT or HCPCS codes have been assigned to Skysona (elivaldogene autotemcel) and its administration.

Code	Description

J3590	Unclassified biologic
C9399	Unclassified drug or biologic (Medicare hospital outpatient use only)

ICD-10-CM Diagnosis Code	Description
E71.520	Childhood cerebral X-linked adrenoleukodystrophy

MassHealth ACO members

Skysona is listed on the **MassHealth Acute Hospital Carve-Out Drugs List**. Hospitals should review the **Acute Hospitals - Billing instructions for Carve-Out Drugs** posted on the "Billing Tips" section of the MassHealth website.

In accordance with **MassHealth All Provider Bulletin 366** (May 2023), effective November 15, 2023, payment will only be made for Skysona when providers use non-340B stock.

In accordance with **MassHealth Managed Care Entity Bulletin 42** (September 2020), Fallon Health requires hospitals to take the following actions with respect to drugs and biologics (including CAR T-cell therapies) on the MassHealth Acute Hospital Carve-Out List for MassHealth ACO members:

1. Drugs and biologics on the MassHealth Acute Hospital Carve-Out Drugs List require prior authorization. The hospital must obtain prior authorization for the drug or biologic from Fallon Health or our designated pharmacy vendor. This prior authorization is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter.
2. A drug or biologic designated by MassHealth as a carve-out drug must not be included on the facility/institutional claim that the hospital submits for the plan member's inpatient or outpatient encounter.
3. The hospital must instead submit a separate claim for the carve-out drug on a facility/institutional claim form (i.e., UB-04). (In other words, the drug is the only item on the UB-04 claim.) The charge reported on the claim must be the "hospital's actual acquisition cost" for the drug.*
4. The claim for the carve-out drug must be reported with revenue code 0636 (Drugs requiring detailed coding), the HCPCS code for the drug, the National Drug Code (NDC) for the drug, and number of units administered.
5. The hospital must also include the following as separate attachments to the claim:

a. A statement of the hospital's actual acquisition cost of the carve-out drug (as defined below) used to treat the member; and
b. A copy of the invoice(s) for the carve-out drug from the drug manufacturer, supplier, distributor, or other similar party or agent; and
c. Other additional documentation that the Plan deems necessary to evidence the hospital's actual acquisition cost of the carve-out drug.

* For purposes of this requirement, the "hospital's actual acquisition cost" of the carve-out drug is defined as follows:
"…*the hospital's invoice price for the drug, net of all on-or-off invoice reductions, discounts, rebates, charge backs and similar adjustments that the hospital has or will receive from the drug manufacturer or other party for the drug that was administered to the member including any efficacy, outcome, or performance-based guarantees (or similar arrangements), whether received pre-or post-payment*."

Policy history

Origination date:	03/01/2024
Approval(s):	Technology Assessment Committee: 07/25/2023 (policy origination)

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.