Molina Clinical Policy
Kebilidi (eladocagene exuparvovec): Policy No. 461

Last Approval: 12/11/2024
Next Review Due By: December 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy covers the use of Kebilidi (eladocagene exuparvovec) for the treatment of individuals with Aromatic L-amino acid decarboxylase deficiency (AADC).

Aromatic L-amino acid decarboxylase deficiency (AADC) is a rare, neurometabolic disorder resulting from the loss of dopa decarboxylase (DDC) function required to synthesize neurotransmitters (dopamine and serotonin). Symptomatology of AADC begins in the first 6 months of life and includes developmental delay, cognitive issues (intellectual disability), behavioral issues (anxiety, autistic features) and motor issues (dystonia, hypokinesia, oculogyric crises) as well as autonomic dysfunction (temperature instability, hypoglycemia). Diagnosis of AADC is based on three key diagnostic elements (Wassenberg et al. 2017). The first element is a specific biochemical profile on CSF analysis*. The second element is genetic testing revealing pathogenic DDC gene variants and, the third element is a decreased plasma AADC enzyme activity. Mild diffuse atrophy and / or delayed myelination can be seen on brain MRI. AADC symptoms can range from mild to severe. Most patients with AADC are severe and have a high risk of death by 5 to 6 years of age due to severe motor dysfunction (Blau et al. 2023).

AADC is an autosomal recessive condition. This means AADC results when two copies of the DDC gene (dopa decarboxylase gene) are inherited with disease causing mutations. Incidence of AADC is estimated to be 1 to 3 per 1,000,000 live births (Blau et al. 2024). Half of the cases occur in those of Asian ancestry and many of those cases occur in patients with Taiwanese ancestry. There are no disease modifying treatments for AADC other than supportive care. Therapies aimed at increasing neurotransmitter production or decreasing destruction of neurotransmitters (inhibition of monoamine oxidase) have been tried but without tremendous success.

Kebilidi is a recently approved viral vector-based gene therapy using the rAAV2 (recombinant adeno-associated viral vector serotype 2) to deliver a functional copy of the dopa decarboxylase gene to a patient. It is the first approved gene therapy administered directly to the brain via stereotactic surgery. Once infused into the putamen, the AADC enzyme is expressed, and dopamine production occurs. The FDA's accelerated approval was based in part on positive outcomes from a phase I / II study of eladocagene in 10 patients with severe AADC deficiency. The primary endpoint, PDMS-2 (Peabody Development Motor Scales, second edition), showed meaningful improvement in all trial participants receiving the therapy (Tai et al. 2021, Chien et al. 2017). Per manufacturer, the procedure for gene therapy delivery is approximately 8 hours and patients remain in the hospital for 3-4 days post operatively.

*CSF biochemical profile suggestive of AADC: low 5-HIAA [5-hydroxyindoleacetic acid], HVA [homovanillic acid], and MHPG [3-methoxy-4-hydroxyphenylglycol], normal pterins and elevated 3-OMD [3-O-methyldopa], L-Dopa [L-3,4-hihydoxyphenylalanine], 5-HTP [5-hydroxytryptophan].

COVERAGE POLICY

<u>All Gene Therapy requests require Molina Medical Director review.</u>

Kebilidi (**eladocagene exuparvovec**) may be **considered medically necessary** when ALL the following criteria are met:

1. Pediatric participants must have genetically confirmed AADC deficiency with typical clinical characteristics and decreased AADC enzyme activity in plasma or a CSF biochemical profile consistent with AADC

2. Member's cranium must be sufficiently developed to allow placement of ClearPoint® system for stereotactic surgery, confirmed by neuroimaging (cranium development sufficient to deliver therapy is usually present in the age range of 16 -24 months)

3. Member has persistent neurological deficits related to AADC deficiency despite standard medical therapy (dopamine agonists, monoamine oxidase inhibitor, pyridoxine, or other forms of vitamin B6)

4. Member is unable to ambulate independently (with or without assistive device)

5. Member's baseline hematology, chemistry, and coagulation values are within the normal limits

6. Member must test negative for coronavirus disease of 2019 (COVID-19) a maximum of 72 hours prior to receiving gene therapy

7. Prior to eladocagene therapy member must be on stable doses of all medications related to treatment of AADC deficiency, including dopamine agonists, monoamine oxidase inhibitors, anticholinergic drugs, and vitamin B6

8. Females of childbearing potential must have a negative pregnancy test at screening and baseline and agree to abstinence or double-barrier form of contraception prior to gene therapy infusion

9. Males sexually active with females of childbearing potential must agree to use a barrier method of birth control prior to gene therapy infusion

10. The participant does not have significant medical or neurological conditions that create an unacceptable operative or anesthetic risk

11. Member does not have pyridoxine 5'-phosphate oxidase or tetrahydrobiopterin (BH4) deficiency

12. Member does not have contraindication to imaging studies (computed tomography [CT] scan, PET or magnetic resonance imaging [MRI]), including sedation limitations or metal that would interfere with a brain MRI

13. Member does not have anti-adeno-associated virus, serotype 2 (anti-AAV2) antibody titer higher than 1:1200 or >1 optical density value by enzyme-linked immunosorbent assay

14. Member has not had treatment with other experimental therapies within the last 24 weeks prior to gene therapy administration, or any treatment ever with a gene therapy

15. Member does not have evidence of a clinically active infection

16. Member is not breast feeding

LIMITATIONS AND EXCLUSIONS

QUANTITY LIMITATIONS: FDA approved dosing with one-time dose per lifetime. Additional infusions of Kebilidi will not be authorized.

CONTINUATION OF THERAPY

Kebilidi (Eladocagene Exuparvovec) is indicated as a one-time infusion only. Repeat treatment or re-administration of a dose is not supported by labeling or compendia and is not considered medically necessary.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the

documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The primary source of data for accelerated FDA approval was clinical trial PTC-AADC-GT-002 [NCT04903288]. This was a single arm, open label study with ages ranging from 16 months to 10 years. The median age was 2.8 years. Thirteen patients received eladocagene 12 of which had a severe phenotype: no motor milestone achievement at baseline & no response to standard therapies. Milestones were assessed at baseline and at week 48. One patient dropped out prior to week 48. Of the 12 remaining participants 8 acquired a new gross motor milestone at week 48, the 4 patients who were unable to make gains were treated between ages 2.8 - 10 years of age (FDA package insert, 2024). None of the external controls had achieved new motor milestones at last assessment (age range from 2-19 years of age). Other trials described below have noted additional gains after 24 months post treatment.

A long-term study (Tai et al. 2021) assessed safety and efficacy of eladocagene treatment in AADC by combining data from three trials (compassionate use [AADC-CU/1601], phase 1 / 2 [NCT01395641], and phase 2b [NCT02926066]). All trials were single arm, open label trials. The primary difference among the trials was in the phase 2b trial that limited enrollment to patients aged 6 or younger and shifted to a higher dose of eladocagene by 33%. The compassionate use study involved eight patients, the phase 1 / 2 trial enrolled ten patients, and the phase 2b trial enrolled eight patients. A combined total of 26 patients with severe AADC (without head control) received bilateral intra-putaminal infusions of eladocagene at a mean age of 4.1 years (range 1.7-8.5 years), mean follow-up period was 5.4 years (range 2.0-10.2 years). Eladocagene therapy showed rapid improvements in motor and cognitive function within 12 months that were sustained over 5 years. The clinical Improvements included significant increases in motor function scores as measured by PDMS-2 and AIMS scaled scores (PDMS2 – Peabody Developmental Motor Scales second edition; AIMS- Alberta Infant Motor Scale). Baseline PDMS-2 was 10.4 which improved to 80.5 by year 1 and 116.1 by year 5 ($p< 0.01$) post eladocagene therapy. AIMS core increased from 1.8 to 24.5 at year 5 post treatment. Three patients achieved independent walking.

Also statistically significant were improved cognitive and language abilities per Bayley-III scores. One patient developed speech capabilities. Body weight gain improved from 26% in first year vs 9.4% pre-treatment. Lastly, oculogyric crises decreased as did excessive sweating and temperature instability. Laboratory data improvements included increased CSF HVA levels (from 6.6 to 30.2 nmol/L at 12 months), enhanced dopamine production shown through PET imaging, and sustained AADC enzyme activity in the putamen. Eleven patients from these three combined trials, who had been followed for >5 years showed sustained improvements as noted by maintenance of motor and cognitive gains and stable PET imaging results at 5 years.

There were two deaths reported among the trial participants. One patient experienced encephalitis secondary to influenzae B, eleven months after receiving eladocagene therapy and died. There was an endemic outbreak of influenzae B at the time and this death was reported to be unrelated to the therapy. The other patient died of probable aspiration 5 years after receiving eladocagene therapy. The most common side effects were dyskinesia (24 patients), pyrexia, upper respiratory tract infections and CSF leakage related to surgery and were managed with standard therapy. Most dyskinesia events resolved within months and are believed to be related to dopamine receptor sensitivity after prolonged deficiency of dopamine. There were no new significant safety concerns in long-term follow-up. Prognostic factors suggesting a better response to eladocagene were younger age at treatment and higher pre-treatment HVA levels. There was no correlation between dosage and treatment outcomes. In addition to patient benefit, caregivers reported improved quality of life across multiple domains including physical health, psychological well-being, and social relationships. Of note, there was only 1 adult (19 years old) treated in any of the clinical trials.

An economic modeling study comparing best supportive care (n= 49) versus eladocagene therapy (n = 30) was reported in 2023 (Simons et al. 2023). Best supportive therapies included dopamine agonists, monoamine oxidase inhibitors, pyridoxal phosphate/pyridoxine, anticholinergic agents, folic acid, L-dopa (with or without carbidopa), 5-hydroxytryptophan, benzodiazepines, melatonin, and selective serotonin-reuptake inhibitors. The best supportive care was delivered via guidelines developed by the international working group on neurotransmitter related disorders. There were 2 patients out of 49 that gained more than one motor milestone, but otherwise, the standard of care approach did not appear to improve motor function or help individuals attain milestones. Estimates suggest an additional 25.25 life years were gained and 20.21 quality-of-life-benefits were gained for the eladocagene group compared to the best supportive care group.

One additional clinical trial NCT04903288 not yet completed is a long-term extension study designed to capture long-term safety and efficacy data from participants treated with eladocagene exuparvovec.

National/Specialty Organizations

The **National Institute for Health and Care Excellence (NICE)** published guidelines recommend eladocagene for people with severe AADC at 18 months of age and over. "The clinical evidence suggests that eladocagene exuparvovec improves motor development, and that these improvements will last."

The **National Organization of Rare Disorders** published guidelines for the treatment of AADC (Wasserman et al. 2017). However, at the time of guideline publication in 2017, eladocagene was not yet available.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
64999	Unlisted procedure, nervous system [when specified as stereotactic placement of infusion catheter(s) in the brain for delivery of therapeutic agent(s)]

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
C9399	Unclassified drugs or biologicals [when specified as Kebilidi (eladocagene exuparvovec)]
J3590	Unclassified biologics [when specified as Kebilidi (eladocagene exuparvovec)]

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and 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. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/11/2024 New policy. IRO review completed December 2024 by a practicing physician board certified in neurology.

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