Oscar Clinical Guideline: Kebilidi (eladocagene exuparvovec-tneq) (PG259, Ver. 2)

Kebilidi (eladocagene exuparvovec-tneq)

Summary

Aromatic L-amino acid decarboxylase deficiency (AADCD) is a rare, autosomal, recessive disorder due to biallelic mutations in the DOPA decarboxylase (DDC) gene. This leads to a deficiency in the aromatic L-amino acid decarboxylase (AADC) enzyme, which leads to deficiencies in dopamine, epinephrine, norepinephrine, and serotonin.

AADCD is classified into three main phenotypes: mild, moderate, and severe. The severe phenotype describes individuals who have no development in motor milestones, have severe cognitive impairment, and are completely dependent on caregivers for aspects of daily living. Additionally, these individuals have severe hypotonia, feeding difficulties, dystonic movements, and autonomic dysfunction. These individuals experience early mortality in childhood. The mild phenotype describes individuals who have less gross motor impairment and can ambulate independently. Some can live into adulthood, may not have any motor impairments, and experience primarily autonomic dysfunction. The moderate phenotype describes individuals who can achieve some motor milestones (i.e., head control, sitting, standing) but are unable to master independent ambulation.

Standard of care therapies include the use of dopamine agonists, monoamine oxidase inhibitors (MAOIs), and pyridoxine (vitamin B6).

Kebilidi (eladocagene exuparvovec-tneq) is a recombinant adeno-associated virus serotype 2 (AAV2)-based gene therapy product that contains a copy of the human DDC gene. A single dose of 1.8×10^{11} vg is administered over four (4) intraputaminal infusions utilizing SmartFlow® Cannula (manufactured by ClearPoint Neuro) during a single stereotactic neurosurgical procedure. This indication is approved under accelerated approval based on change from baseline in gross motor milestone achievement at 48 weeks post-treatment. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

Definitions

"Ambulate" means to walk or move about. Individuals with severe AADCD are unable to ambulate independently and are dependent on caregivers for activities of daily living.

"Biallelic mutations" are disease-causing mutations present in both copies (maternal and paternal) of a gene, in this case the DDC gene.

"Cerebrospinal fluid", also known as (CSF), is an ultrafiltrate of plasma that circulates around the hollow spaces of the brain and spinal cord. CSF is a mixture of several metabolites, including neurotransmitters. Lumbar puncture is the most common method to collect CSF.

"Clearpoint system", manufactured by ClearPoint Neuro, utilizes SmartFlow® Cannula to administer Kebilidi (eladocagene exuparvovec-tneq) over four intraputaminal infusions in a single stereotactic neurosurgical procedure.

"Cognitive impairment" in AADCD manifests as a developmental delay such as having difficulty speaking and learning.

"Compound heterozygous" is two different mutant alleles at a given locus (location of the gene on a region of a chromosome).

"Compound homozygous" is identical mutant alleles at a given locus (location of the gene on a region of a chromosome).

"Documentation" refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"Motor milestones", are part of developmental milestones that most children are able to do by a certain age. Motor milestones include head control, sitting, standing, and walking. The Peabody Developmental Motor Scale, second edition (PDMS-2) is one tool to assess motor milestones.

"[s]" indicates state mandates may apply.

Clinical Indications

Medical Necessity Criteria for Clinical Review

Indication-Specific Criteria

Aromatic L-amino Acid Decarboxylase (AADC) Deficiency

The Plan considers Kebilidi (eladocagene exuparvovec-tneq) medically necessary when ALL of the following criteria are met:

1. The medication is prescribed by or in consultation with a pediatric neurologist; *AND*
2. The member is 16 months to 10 years of age; *AND*
3. The member has a diagnosis of aromatic L amino acid decarboxylase deficiency (AADCD).
4. Genetic testing showing biallelic mutations in the DOPA decarboxylase (DDC) gene and TWO (2) of the following are met:
    a. Low cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4- hydroxyphenylglycol (MHPG), increased CSF levels of 3-O-methyldopa (3-OMD), L-Dopa and 5-OH tryptophan (5-HTP), and normal CSF pterins (neopterin, dihydrobiopterin and tetrahydrobiopterin); *and/or*

b. Compound heterozygous OR homozygous pathogenic variants in the DOPA decarboxylase (DDC) gene; *and/or*
c. Decreased aromatic L-amino acid decarboxylase (AADC) enzyme activity in the plasma; *and*

5. The member's AADCD is classified as severe and meets ALL of the following:
    a. Unable to achieve any motor milestones; *and*
    b. Limited to poor or no head control; *and*
    c. Unable to ambulate independently (with or without assistive devices); *and*
    d. Cognitive impairment; *and*
6. The member's cranium is sufficiently developed (i.e., fully mature skull, without open sutures, and sufficient skull thickness evaluated by skull imaging) to allow placement of ClearPoint system for stereotactic surgery; *AND*
7. The member is unable to use, or has tried and failed ALL of the following[s]:
    a. Dopamine agonist (e.g., pramipexole, ropinirole, rotigotine); *and*
    b. MAO inhibitor (e.g., tranylcypromine, selegiline, phenelzine); *and*
    c. Pyridoxal phosphate or pyridoxine (vitamin B6); *and*
8. The member meets ALL of the following:
    a. No pre-existing anti-AAV2 neutralizing antibody at titers >1:1200; *and*
    b. No pyridoxine 5'-phosphate oxidase or tetrahydrobiopterin deficiency; *and*
    c. No prior treatment with gene therapy; *and*
9. Kebilidi (eladocagene exuparvovec-tneq) is being prescribed at a dose and frequency that is within FDA approved labeling.

<u>If the above prior authorization criteria are met, the requested product will be authorized for one dose per lifetime, with an approval duration of up to 6 months.</u>[s]

Experimental or Investigational or Unproven/ Not Medically Necessary[s]

Kebilidi (eladocagene exuparvovec-tneq) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, unproven, or not medically necessary. Non-covered indications include, but are not limited to, the following:

- Re-treatment - Kebilidi (eladocagene exuparvovec-tneq) is indicated as four intraputaminal infusions in a single stereotactic neurosurgical procedure gene therapy only.
- Use in individuals greater than 10 years of age. Kebilidi (eladocagene exuparvovec-tneq) has not been studied in those 10 years of age and older.
- Treatment of mild or moderate phenotypes of AADCD. Kebilidi (eladocagene exuparvovec-tneq) has only been studied in those with a severe phenotype of AADCD.
- Non-motor manifestations of AADCD. Because Kebilidi (eladocagene exuparvovec-tneq) has only been studied in those with a severe phenotype of AADCD, those with non-motor manifestations of AADCD were not included in the original clinical study.

Rationale: Kebilidi (eladocagene exuparvovec-tneq) has not been adequately studied for safety and efficacy in the above patient populations and clinical scenarios.

- In its pivotal trial (AADC-002, NCT04903288) that enrolled pediatric patients aged 16 months to 10 years, the primary endpoint was change from baseline in homovanillic acid (HVA) levels, a byproduct of dopamine breakdown, 8 weeks after administration. Its secondary endpoint was motor development as assessed by the PDMS-2 at week 48.
- No efficacy data were submitted on patients with other AADCD phenotypes (mild and moderate).
- There is uncertainty in the efficacy of Kebilidi (eladocagene exuparvovec-tneq) on the non-motor manifestations of AADCD as the pivotal trial assessed gross motor milestone achievement and there is insufficient evidence to support extrapolation for other AADCD manifestations.
- No efficacy data were submitted to assess the benefit-risk in adults, including the appropriateness of the intended dose in an adult population with AADCD. As such, there is uncertainty as to whether adolescents and adults retain enough neuroplasticity to benefit from Kebilidi (eladocagene exuparvovec-tneq). Additional data are needed to inform a benefit-risk determination and an appropriate dosage regimen in adults with AADCD.
- The above Plan positions are based on the best currently available clinical evidence for Kebilidi (eladocagene exuparvovec-tneq) in AADCD. As additional trials are published, the Plan will modify these policy statements accordingly to reflect any relevant changes in the evidence base and/or guideline recommendations.

Applicable Billing Codes

Table 1	
CPT/HCPCS codes considered medically necessary if criteria are met:	
Code	*Description*
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics

Table 2	
ICD-10 codes considered medically necessary with Table 1 codes if criteria are met::	
Code	*Description*
E70.81	Aromatic L-Amino Acid Decarboxylase Deficiency

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Clinical Guideline Revision / History Information

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