Luxturna (voretigene neparvovec-rzyl)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

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 Luxturna (voretigene neparvovec-rzyl) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. 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

Luxturna is indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).

POLICY

Required Documentation

A. Genetic testing confirming presence of bilallelic RPE65 pathogenic variant(s) or likely pathogenic variants (see Appendix for additional details)
B. Documentation, imaging, and/or tests confirming presence of viable retinal cells as determined by treating physicians as assessed by optical coherence tomography imaging and/or ophthalmoscopy

Criteria for Initial Approval

A. Luxturna (voretigene neparvovec-rzyl) may be considered **medically necessary** for the treatment of Biallelic RPE65 mutation-associated retinal dystrophy in members who meet the following criteria:
    1. The medication must be prescribed and administered by an ophthalmic surgeon at a certified treatment center
    2. The member is ≥12 months and <65 years of age at the time of administration of Luxturna

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3. The member has genetic testing confirming the presence of biallelic pathogenic and/or likely pathogenic RPE65 variant(s)
    a. Single RPE65 pathogenic variant or likely pathogenic variant found in the homozygous state
    b. Two RPE65 pathogenic variants or likely pathogenic variants found in the trans configuration (compound heterozygous state) by segregation analysis
4. Presence of viable retinal cells as determined by treating physicians as assessed by optical coherence tomography imaging and/or ophthalmoscopy:
    a. An area of retina within the posterior pole of greater than 100 µm thickness shown on optical coherence tomography, OR
    b. 3 or more disc areas of retina without atrophy or pigmentary degeneration within the posterior pole, OR
    c. Remaining visual field within 30 degrees of fixation as measured by III4e isopter or equivalent
5. The member does not have any of the following:
    a. Pregnancy in females
    b. Breastfeeding
    c. Use of high dose (>7500 retinol equivalent units [or >3300 IU] per day of vitamin A) retinoid compounds in the past 18 months
    d. Intraocular surgery within 6 months
    e. Prior RPE65 gene therapy in the intended eye
6. Preexisting eye conditions or complicating systemic diseases that would interfere with this gene therapy including but not limited to:
    a. Malignancies whose treatment could affect central nervous system function (e.g., radiotherapy of the orbit; leukemia with central nervous system/optic nerve involvement)
    b. Retinopathy associated with diabetic macular edema or sickle cell disease
    c. Immunodeficiency (acquired or congenital) making the member susceptible to opportunistic infection (e.g., cytomegalovirus retinitis)

Approval will be for **6 months (1 treatment course of 1 injection per eye per lifetime).**

Lifetime Limits Apply

- 1 injection per eye

Dosing and Administration

- The recommended dose of voretigene neparvovec-rzyl for each eye is 1.5×1011 vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL
- Subretinal administration of voretigene neparvovec-rzyl to each eye must be performed on separate days within a close interval, but no fewer than 6 days apart
- Systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/d (maximum, 40 mg/d) recommended for a total of 7 days (starting 3 days before administration of voretigene neparvovec- rzyl to each eye), and followed by a tapering dose during the next 10 days

APPENDIX

Diagnosis of Biallelic RPE65-Mediated Inherited Retinal Dystrophies

Genetic testing is required to detect the presence of pathogenic or likely pathogenic variants in the RPE65 gene in individuals with documented vision loss. By definition, pathogenic or likely pathogenic variant(s) must be present in both copies of the RPE65 gene to establish a diagnosis of biallelic RPE65-mediated inherited retinal dystrophy.

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A single RPE65 pathogenic or likely pathogenic variant found in the homozygous state (e.g., the presence of the same pathogenic or likely pathogenic variant in both copies alleles of the RPE65 gene) establishes a diagnosis of biallelic RPE65-mediated dystrophinopathy.

However, if 2 different RPE65 pathogenic or likely pathogenic variants are detected (e.g., compound heterogygous state), confirmatory testing such as segregation analysis by family studies may be required to determine the trans vs cis configuration (e.g., whether the 2 different pathogenic or likely pathogenic variants are found in different copies or in the same copy of the RPE65 gene). The presence of 2 different RPE65 pathogenic or likely pathogenic variants in separate copies of the RPE65 gene (trans configuration) establishes a diagnosis of biallelic RPE65-mediated dystrophinopathy. The presence of 2 different RPE65 pathogenic or likely pathogenic variants in only 1 copy of the RPE65 gene (cis configuration) is not considered a biallelic RPE65-mediated dystrophinopathy.

Next-generation sequencing and Sanger sequencing typically cannot resolve the phase (e.g., trans vs cis configuration) when two RPE65 pathogenic or likely pathogenic variants are detected. In this scenario, additional documentation of the trans configuration is required to establish a diagnosis of biallelic RPE65-mediated inherited retinal dystrophy. Table PG1 provides a visual representation of the genetic status requirements to establish a diagnosis of RPE65-mediated inherited retinal dystrophy.

Table 1. Genetic Diagnosis of RPE65-Mediated Inherited Retinal Dystroph

Genetic Status	**Diagram**	**Diagnosis of RPE65-Mediated Inherited Retinal Dystrophy?**
Homozygous	RPE65 gene copy #1 (- - - - - - **X** - - - - - -) RPE65 gene copy #2 (- - - - - - **X** - - - - - -) **X**=single RPE65 pathogenic or likely pathogenic variant	Yes
Heterozygous (trans configuration)	RPE65 gene copy #1 (- - - - - - **X** - - - - - -) RPE65 gene copy #2 (- - - **O** - - - - - - - - -) **X**=RPE65 pathogenic or likely pathogenic variant #1 O=RPE65 pathogenic or likely pathogenic variant #2	Yes
Heterozygous (cis configuration)	RPE65 gene copy #1 (- - **O** - - **X** - - - - - -) RPE65 gene copy #2 (- - - - - - - - - - - - -) **X**=RPE65 pathogenic or likely pathogenic variant #1 **O**=RPE65 pathogenic or likely pathogenic variant #2	No

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

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The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table 2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table 3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

- J3398 Luxturna, Injection, voretigene neparvovec-rzyl, 1billion vector genome

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