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 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
    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

CLINICAL RATIONALE

Inheritable retinal dystrophies are rare conditions caused by a gene mutation leading to blindness. The most common subtypes include retinitis pigmentosa and Leber congenital amaurosis. This form of retinal dystrophy is characterized by an earlier onset and more rapid progression than other retinal dystrophies and result in nyctalopia and loss of peripheral vision. These retinal dystrophies are often associated with biallelic mutations of the RPE65 gene which results in reduced or absent RPE65 enzymes. This deficiency results in the build-up of toxic precursors causing photoreceptor-cell dysfunction, loss, and eventual blindness.

Luxturna is an adeno-associated virus vector-based gene therapy that delivers a normal copy of the RPE65 gene to retinal cells. It was approved by the FDA on December 19, 2017 for use in patients with vision loss due to confirmed biallelic RPE65 variant-associated retinal dystrophy.

A phase III, randomized, controlled, open-label trial sought to assess the efficacy and safety of Luxturna (voretigene-neparvovec) in individuals with RPE-65 mediated inherited retinal dystrophy. A total of 31 patients, between 3 and 65 years of age, were included in the study. Participants had a confirmed genetic diagnosis of biallelic RPE65 gene mutations, a visual acuity of 20/60 or worse for both eyes or a visual field of less than 20 degrees in any meridian, and sufficient viable retinal cells as determined by retinal thickness on spectral domain optical coherence tomography (>100 microns within the posterior pole). Participants were randomized 2:1, with 21 receiving the intervention and 10 the control. After 1 year, participants within the control group were eligible to receive treatment, provided they still met the criteria. The intervention group received a subretinal injection of 1.5x1011 vg of voretigene-neparvovec in 0.3 mL in one eye initially. After 6-18 days, the second eye received the same treatment. Efficacy assessments occurred on days 30, 90, 180, and 365. The primary outcome was the change in bilateral multi-luminance mobility test (MLMT) 1 year from baseline. A change of 1 or more lux levels was considered clinically significant. The MLMT was designed as a navigational course to assess participants' ability to navigate around obstacles in variable light conditions. Secondary outcomes included full-field light sensitivity threshold (FST) and best-corrected visual acuity (BCVA). Analyses were performed based upon intention-to-treat. A statistically significant difference was found between the treatment and control groups for the primary outcome. One year from baseline, the mean change in MLMT score of the treatment group was 1.8, compared to 0.2 for the control group. Improvements in MLMT occurred for 18 of 20 patients receiving the intervention, with 13 of 20 achieving the maximum MLMT score. Statistical significance was also reached for the secondary outcomes. A mean improvement of FST by 2 log units occurred in the treatment group compared to no change in the control group. BCVA scores improved by 8.1 letters on the eye chart for the treatment group compared to 1.6 letters for the control. No serious adverse events occurred, with the most common adverse events including transient mild ocular inflammation, transient elevated intraocular pressure, and intraoperative retinal tears.

A subsequent follow-on study from the aforementioned phase III clinical trial sought to assess the efficacy and safety of Luxturna (voretigene-neparvovec) at 1 year post-administration. Both the original and control/intervention groups were followed for 1 year post-administration, and in each group an average improvement in FST by 2 log units (1.9[1.0] original, 2.1[1.6] control) was maintained for the entire duration of the trial. The safety profile was consistent with vitrectomy and the subretinal injection procedure, and no deleterious immune responses occurred. Observation continues to be ongoing.

Based upon the clinical trials, Luxturna appears to be effective in restoring RPE65 activity, leading to clinically significant improvements in vision for patients with RPE65-mediated inherited retinal dystrophy. Luxturna has also been shown to have an acceptable safety profile.

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.

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 vscis 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 Hman Genome Organization, and by the Human Genome Variation Society itself.

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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