Voretigene Neparvovec-rzyl (Luxturna™)

Description of Procedure or Service

Voretigene neparvovec-rzyl (Luxturna) is an adeno-associated virus vector-based gene therapy 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).

Inherited Retinal Dystrophies

Inherited retinal dystrophies (IRDs) are a diverse group of disorders with overlapping phenotypes characterized by progressive degeneration and dysfunction of the retina. The most common subgroup is retinitis pigmentosa, which is characterized by a loss of retinal photoreceptors, both cones and rods. The hallmark of the condition is night blindness (nyctalopia) and loss of peripheral vision. These losses lead to difficulties in performing visually dependent activities of daily living such as orientation and navigation in dimly lit areas. Visual acuity may be maintained longer than peripheral vision, though eventually, most individuals progress to vision loss.

RPE65 Gene

Retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA) both have subtypes related to pathogenic variants in RPE65. RPE65 (retinal pigment epithelium–specific protein 65-kD) gene encodes the RPE54 protein, an all-trans retinal isomerase, a key enzyme expressed in the retinal pigment epithelium (RPE) that is responsible for regeneration of 11-cis-retinol in the visual cycle. The RPE65 gene is located on the short (p) arm of chromosome 1 at position 31.3 (1p31.3). Individuals with biallelic variations in RPE65 lack the RPE65 enzyme; this lack leads to build-up of toxic precursors and damage to RPE cells, loss of photoreceptors, and eventually complete blindness.

Epidemiology

RPE65-associated IRD is rare. The prevalence of LCA has been estimated to be between 1 in 33,000 and 1 in 81,000 individuals in the United States. LCA subtype 2 (RPE65-associated LCA) accounts for between 5% and 16% of cases of LCA. The prevalence of RP in the United States is approximately 1 in 3500 to 1 in 4000 with approximately 1% of patients with RP having RPE65 variants. Assuming a U.S. population of approximately 326.4 million at the end of 2017, the prevalence of RPE65-associated retinal dystrophies in the United States would, therefore, be roughly 1000 to 2500 individuals.

Gene Therapy

Gene therapies are treatments that change the expression of genes to treat disease, eg, by replacing or inactivating a gene that is not functioning properly or by introducing a new gene. Genes may be introduced into human cells through a vector, usually a virus. Adeno-associated viruses (AAV) are frequently used due to their unique biology and simple structure. These viruses are in the parvovirus family and are dependent on coinfection with other viruses, usually adenoviruses, to replicate. AAVs are poorly immunogenic compared with other viruses but can still trigger immune response making it a challenge to deliver an effective dose without triggering an immune response that might render the gene therapy ineffective or harm the patient. There are over 100 different AAVs and 12 serotypes have been
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identified so far, labeled AAV1 to AAV12; in particular, AAV2, AAV4, and AAV5 are specific for retinal tissues. The recombinant AAV2 is the most commonly used AAV serotype in gene therapy. The eye is a particularly appropriate target for gene therapy due to the immune privilege provided by the blood-ocular barrier and the minimal amount of vector needed, given the size of the organ. Gene therapy for RPE65 variant-associated retinal dystrophy using various AAV vectors to transfected cells with a functioning copy of RPE65 in the RPE cells has been investigated.

**Regulatory Status**

On December 19, 2017, the AAV2 gene therapy vector voretigene neparvovec-rzyl (Luxturna™; Spark Therapeutics) was approved by the U.S. Food and Drug Administration (FDA) for use in patients with vision loss due to confirmed biallelic RPE65 variant-associated retinal dystrophy. Spark Therapeutics received breakthrough therapy designation, rare pediatric disease designation, and orphan drug designation.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

BCBSNC will provide coverage for Voretigene Neparvovec-rzyl (Luxturna) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

**Benefits Application**

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**When Voretigene neparvovec-rzyl (Luxturna) is covered**

Voretigene neparvovec-rzyl (Luxturna) gene therapy subretinal injection is considered medically necessary for the treatment of vision loss due to RPE65 variant-associated retinal dystrophy, if all of the following criteria are met:

- The individual is ≥3 and <65 years of age;
- There is documentation of the following:
  - A. Genetic testing confirming the presence of biallelic RPE65 mutations (see Policy Guidelines for additional details), AND
  - B. Presence of viable retinal cells as determined by treating physicians as assessed by optical coherence tomography imaging and/or ophthalmoscopy:
    1. An area of retina within the posterior pole of >100 μm thickness shown on optical coherence tomography, OR
    2. ≥3 disc areas of retina without atrophy or pigmented degeneration within the posterior pole, OR
    3. Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent;
- The individual is not pregnant or breastfeeding;
- No prior intraocular surgery within the past 6 months;
- There are no preexisting eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of the study. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (eg, radiotherapy of the orbit; leukemia with central nervous system/optic nerve involvement). Subjects with diabetes or sickle cell disease would be excluded if they have any manifestation of advanced retinopathy (eg, macular edema, proliferative changes). Also
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excluded would be subjects with immunodeficiency (acquired or congenital) because they could be susceptible to opportunistic infection (eg, cytomegalovirus retinitis).

Documentation of sufficient and viable retinal cells must be determined prior to administration.

When Voretigene neparvovec-rzyl (Luxturna) is not covered

Voretigene neparvovec-rzyl (Luxturna) gene therapy subretinal injection is considered not medically necessary and therefore not covered when above criteria are not met.

Other applications of voretigene neparvovec-rzyl (Luxturna) are considered investigational.

Policy Guidelines

For individuals who have vision loss due to biallelic \( RPE65 \) variant-associated retinal dystrophy who receive gene therapy, the evidence includes randomized controlled trials and uncontrolled trials. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Biallelic \( RPE65 \) variant-associated retinal dystrophy is a rare condition and, as such, it is recognized that there will be particular challenges in generating evidence, including recruitment for adequately powered RCTs, validation of novel outcome measures, and obtaining long-term data on safety and durability. There are no other FDA-approved pharmacologic treatments for this condition. One RCT \((N=31)\) comparing voretigene neparvovec with a control demonstrated greater improvements on the Multi-Luminance Mobility Test, which measures the ability to navigate in dim lighting conditions. Most other measures of visual function were also significantly improved in the voretigene neparvovec group compared with the control group. Adverse events were mostly mild to moderate. However, there is limited follow-up available, therefore, the long-term efficacy and safety are unknown. Based on a small number of patients from early phase studies, voretigene neparvovec appears to have durable effects to at least 3 years. Other gene therapies tested in early phase trials have shown improvements in retinal function but variable durability of effect; some patients from 2 cohorts who initially experienced improvements have subsequently experienced declines after 1 to 3 years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Diagnosis of Biallelic \( RPE65 \)-Mediated Inherited Retinal Dystrophies

Genetic testing is required to detect the presence of likely pathogenic or pathogenic(s) variants in the \( RPE65 \) gene. By definition, likely pathogenic or 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 \( RPE65 \) likely pathogenic or pathogenic variant found in the homozygous state (eg, the presence of the same variant in both copies alleles of the \( RPE65 \) gene) establishes a diagnosis of biallelic \( RPE65 \)-mediated dystrophinopathy.

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

Next-generation sequencing and Sanger sequencing typically cannot resolve the phase (eg, \textit{trans} vs \textit{cis} configuration) when two \( RPE65 \) pathogenic variants are detected. In this scenario, additional documentation of the \textit{trans} configuration is required to establish a diagnosis of biallelic \( RPE65 \)-mediated inherited retinal dystrophy.
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Luxturna should be given only to patients who have viable retinal cells as determined by the treating physician(s). Treatment with Luxturna must be done separately in each eye on separate days, with at least six days between surgical procedures. It is administered via subretinal injection by a surgeon experienced in performing intraocular surgery. Patients should be treated with a short course of oral prednisone to limit the potential immune reaction to Luxturna.

The recommended dose of voretigene neparvovec-rzyl for each eye is $1.5 \times 10^{11}$ 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/day (maximum, 40 mg/day) 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina website at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: J3398, 67299, 92134

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


U.S. Food and Drug Administration (FDA). Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm

Senior Medical Director Review 1/2018

Medical Director Review 6/2018

Specialty Matched Consultant Advisory Panel review 6/2018


Specialty Matched Consultant Advisory Panel review 6/2019

Policy Implementation/Update Information

2/23/18 New policy developed. Voretigene Neparvovec-rzyl (Luxturna) adeno-associated virus vector-based gene therapy subretinal injection is considered medically necessary for the
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treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy if criteria are met. Documentation of sufficient and viable retinal cells must be determined prior to administration. References added. Senior Medical Director review 1/2018. (lpr)

6/29/18  Updated “When Covered” section to remove the following statements in items #1 and #2 under criterion part A: “1. Single RPE65 pathogenic variant found in the homozygous state; 2. Two RPE65 pathogenic variants found in the trans-configuration (compound heterozygous state) by segregation analysis.” Updated organization of criteria items in “When Covered” section for further clarity. Added code C9032 to Billing/Coding section effective 7/1/18. Reference added. Medical Director review 6/2018. (krc)

8/10/18  Specialty Matched Consultant Advisory Panel review 6/2018. No change to policy intent. (krc)

12/31/18 Added HCPCS code J3398 and deleted codes C9032, C9399, J3490, and J3590 effective 1/1/19. (krc)

7/16/19  Added Luxturna dosing and administration information within Policy Guidelines. Reference added. Specialty Matched Consultant Advisory Panel review 6/19/2019. No change to policy intent. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.