BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 11/17/20**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 02/20/25**
	CURRENT EFFECTIVE DATE: 02/20/25
	LAST CRITERIA REVISION DATE: 02/15/24
NEXT ANNUAL REVIEW DATE: 1ST QTR 2026	**ARCHIVE DATE:**

GENE THERAPY FOR RETINAL DYSTROPHY:

- **LUXTURNA™ (voretigene neparvovec-rzyl)**

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

- Luxturna (voretigene neparvovec-rzyl) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician who is a retinal specialist with expertise in vitreoretinal surgery
2. Individual is at least 12 months of age and less than 65 years of age
3. Individual has a confirmed diagnosis of vision loss due to biallelic RPE65 variant-associated retinal dystrophy
4. Surgery to be performed in an approved specialized facility with an active ophthalmology practice treating individuals with retinal dystrophies
5. Genetic testing has confirmed presence of **ONE** of the following biallelic RPE65 pathogenic or likely pathogenic variant(s):
   - Single RPE65 pathogenic or likely pathogenic variant found in the homozygous state
   - Two RPE65 pathogenic or likely pathogenic variants found in the trans configuration (compound heterozygous state) by segregation analysis
6. Presence of viable retinal cells as assessed by optical coherence tomography (OCT) imaging and/or ophthalmoscopy with **ONE** of the following:
   - An area of retina within the posterior pole of greater than 100 µm thickness shown on OCT
   - 3 or more disc areas of retina without atrophy or pigmentary degeneration within the posterior pole based on ophthalmoscopy
   - Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent
7. There is no history of prior administration of Luxturna (voretigene neparvovec-rzyl) in the same intended eye
8. Individual does **NOT** have **ANY** of the following:
   - Individual of childbearing potential who is pregnant or unwilling to use effective contraception for 4 months following administration of Luxturna
   - Individual who is breast feeding an infant or child
   - Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme, unless they have been discontinued for 18 months
   - Prior intraocular surgery within the last 6 months
   - Preexisting eye conditions or complicating systemic diseases that would preclude planned surgery or interfere with the efficacy of 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. Individuals with diabetes or sickle cell disease if they have any manifestation of advanced retinopathy (e.g., macular edema, proliferative changes)
c. Individuals with immunodeficiency (acquired or congenital) who could be susceptible to opportunistic infection (e.g., cytomegalovirus retinitis)

Approval duration: Once in a life-time treatment course (2 injections total, 1 injection in each eye)

- Luxturna (voretigene neparvovec-rzyl) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any one or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to*:

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Description:

Luxturna (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of individuals with confirmed biallelic RPE65 variant-associated retinal dystrophy. Luxturna is a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the human RPE65 gene.

Biallelic RPE65 variant-associated retinal dystrophy, is a rare genetic condition. It is one of several eye conditions that result from genetic variants in a set of about 220 genes that control for retinal pigment epithelium-specific 65 kDa protein (RPE65, also known as retinoid isomerohydrolase). Individuals with biallelic variants have difficulty seeing in dim light and have progressive loss of vision.

The RPE65 gene provides instructions for making an enzyme that is essential for normal vision. Variants in the gene lead to reduced or absent levels of RPE65 activity, blocking the visual cycle and resulting in impaired vision. Individuals with biallelic RPE65 variant-associated retinal dystrophy experience a slowly progressive deterioration of vision over time. RPE65-mediated retinal disease starts with rod

photoreceptors and later progresses to the cone photoreceptors in the macula. Dysfunction of rod photoreceptor cells, which are solely reliant on RPE65, causes severely impaired night vision. The function of cone photoreceptor cells, which mediate vision in daylight, are relatively preserved. The deterioration of vision, often during childhood or adolescence, ultimately progresses to complete blindness. Most become completely blind by young adulthood.

A number of inherited retinal diseases are caused by recessive variants in the RPE65 gene that codes for the protein RPE65. Variants that affect both copies of the RPE65 gene cause Leber Congenital Amaurosis, type 2 (LCA2), Early Onset Severe Retinal Dystrophy (EOSRD), Severe Early Childhood-onset Retinal Dystrophy (SECORD), Retinitis Pigmentosa type 20 (RP20) and other phenotypes.

Luxturna works by delivering a normal copy of the RPE65 gene directly to viable retinal cells using gene therapy with an adeno-associated virus vector that expresses RPE65. Individuals must have viable retinal cells. The viral vector transfers intact copies of the RPE65 gene directly behind the retina. The retinal cells then produce the normal protein that converts light to an electrical signal in the retina to restore the individual's vision loss.

Genetic Testing to Diagnose Biallelic RPE65-Mediated Inherited Retinal Dystrophies:

Genetic testing is required to identify the presence of pathogenic or likely pathogenic variants in the RPE65 gene.

Pathogenic and 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 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 heterozygous state), confirmatory testing is 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.

History:	**Date**:	**Activity**:
Pharmacy and Therapeutics Committee	02/20/25	Review without revisions

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Pharmacy and Therapeutics Committee	02/15/24	Review with revisions: criteria; resources
Pharmacy and Therapeutics Committee	02/16/23	Review with revisions
Medical Policy Panel	02/15/22	Review with revisions
Clinical Pharmacist	02/02/22	Review with revisions
Medical Policy Panel	11/10/21	Review without revisions
Medical Policy Panel	11/17/20	Approved guideline
Clinical Pharmacist	10/28/20	Development

Coding:

HCPCS: J3398

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Resources:

Literature reviewed 02/20/25. We do not include marketing materials, poster boards and non-published literature in our review.

1. Banken R, Chapman R, Cramer G, Khan S, Pearson SD, Rind D, et al. Voretigene Neparvovec for Biallelic RPE65-Medicated Retinal Disease: Effectiveness and Value. ICER. February 14, 2018. Accessed December 17, 2024. https://icer.org/wp-content/uploads/2020/10/MWCEPAC_VORETIGENE_FINAL_EVIDENCE_REPORT_02142018.pdf

2. Gardiner MF. Retinitis pigmentosa: Clinical presentation and diagnosis. In: UpToDate, Jacobs DS, Li H (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last update on August 29, 2024. Accessed on December 17, 2024.

3. Gardiner MF. Retinitis pigmentosa: Treatment. In: UpToDate, Jacobs DS, Li H (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last update on April 16, 2024. Accessed on December 17, 2024.

4. Luxturna (voretigene neparvovec-rzyl) prescribing information, revised by Spark Therapeutics Inc. 05/2022 at DailyMed https://dailymed.nlm.nih.gov. Accessed on December 4, 2024.

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Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html