MEDICAL COVERAGE POLICY	
SERVICE:	**Voretigene Neparvovec-rzyl (Luxturna)**
Policy Number:	**249**
Effective Date:	**12/01/2023**
Last Review:	**09/28/2023**
Next Review Date:	**09/28/2024**

Important note
Even though this policy may indicate that a particular service or supply may be considered covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Senior Care members, this policy will apply unless Medicare policies extend coverage beyond this Medical Policy & Criteria Statement. Senior Care policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website.

SERVICE: Voretigene Neparvovec-rzyl (Luxturna™)

PRIOR AUTHORIZATION: Required.

POLICY:

For Medicare plans, please refer to appropriate Medicare coverage policies at CMS.gov (e.g. Local Coverage Determination (LCD) documents and Articles, National Coverage Determination (NCD) documents, etc.). If there is no applicable Medicare coverage policy, then use this policy.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid TMPPM. Texas Mandate HB1584 is applicable for Medicaid plans.

For all other plans, BSWHP may find Voretigene Neparvovec-rzyl medically necessary in the treatment of inherited retinal diseases when the following conditions are met:

- Member is between 12 months and 65 years of age; AND
- Has diagnosis of a confirmed biallelic RPE65 mutation-associated retinal dystrophy (e.g. Leber's congenital amaurosis [LCA], retinitis pigmentosa [RP] early onset severe retinal dystrophy [EOSRD], etc.); AND
- Genetic testing documents biallelic mutations of the RPE65 gene; AND
- Member has sufficient viable retinal cells as determined by the treating physician(s) using one of the following criteria:
  - ✓ An area of retina within the posterior pole of >100 um thickness shown on optical coherence testing
  - ✓ Greater than or equal to 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole
  - ✓ Remaining visual field within 30 degrees of fixation as measured by a lll4e isopter or equivalent (both eyes)
- Member has had NO intraocular surgery within 6 months in either eye that is indicated for treatment; AND
- Systemic corticosteroids equivalent to prednisone 1 mg/kg/day are administered for a total of 7 days, starting 3 days before administration of Voretigene Neparvovec-rzyl to each eye and followed by a tapering dose; AND
- Voretigne Neparvovec-rzyl is prescribed and administered by ophthalmologist or retinal surgeon with experience providing sub-retinal injections; AND

- Member has not previously received RPE65 gene therapy in intended eye; AND
- Injection of second eye is at least 6 days from injection of the first eye.

Only ONE injection per eye will be approved per lifetime.

ALL requests for Voretigne Neparvovec-rzyl will be reviewed by both a clinical pharmacist and a medical director.

Voretigene neparvovec (Luxturna™) is considered experimental, investigational, and/or unproven for all other indications.

OVERVIEW:

Inherited retinal diseases (also called inherited retinal dystrophies or IRD) are a group of eye disorders caused by an inherited gene mutation that can result in vision loss or blindness. Some patients impacted by IRDs may experience a gradual loss of vision, others may be born with vision loss or experience vision loss in infancy or early childhood. IRDs are caused by a mutation in 1 of more than 220 different genes, including the RPE65 gene.

The RPE65 gene provides instructions for making a protein that is essential for normal vision produced in the retinal pigment epithelium (RPE), a thin layer of cells at the back of the eye. RPE65 gene mutations lead to a partial or total loss of RPE65 protein function. This loss of function blocks the visual cycle, which leads to severe visual impairment beginning very early in life. Mutations in the RPE65 gene are associated with 2 main types of IRDs: Leber congenital amaurosis and retinitis pigmentosa.

1. Leber congenital amaurosis (LCA) is a group of congenital retinal dystrophies that results in severe vision loss at an early age. Patients usually present with nystagmus, sluggish or near-absent pupillary responses, severely decreased visual acuity, photophobia, and high hyperopia. LCA is the most severe retinal dystrophy, causing blindness by the age of 1 year. The estimated birth prevalence of LCA is 2 to 3 per 100,000 births; it is the most common cause of inherited blindness in childhood.
2. Retinitis pigmentosa (RP) is a group of related eye disorders characterized by progressive vision loss caused by the gradual degeneration of light-sensing cells in the retina. The first sign of RP is usually a loss of night vision, which manifests in childhood. The disease progresses to disrupt peripheral vision and central vision over a period of years. Many people with retinitis pigmentosa become legally blind in adulthood. Mutations in the RPE65 gene are responsible for a small percentage of RP.

There is no cure for IRD. Patients with untreated RPE65-mediated IRD lose the ability to detect light of any intensity over time. Currently no approved pharmacological treatment is available. Thus there is a need for treatment options for RPE65-mediated IRP - Luxturna is a gene therapy proposed to meet this need.

Gene therapy utilizes a viral vector to carry the desired genetic information to target cells. Vectors that are successfully transduced into target cells utilize the cell to express the proteins of interest. The goal of gene therapy is to provide a sustained therapeutic benefit via continual expression of the proteins that modulate the pathogenesis of the relevant disease.

Luxturna is an adeno-associated virus 2 (AAV2) vector containing human RPE65 complementary DNA (cDNA). Luxturna is a one-time therapy. It is injected subretinally under general anesthesia. Patients must have viable retinal cells in order to be treated with Luxturna. Subretinal administration is performed to each eye on separate days within a close interval, but no fewer than 6 days apart. Short-term systemic oral corticosteroids are recommended starting 3 days before administration of Luxturna.

On December 19, 2017, the FDA approved Luxturna for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Luxturna is the first gene therapy approved for the treatment of a genetic disease.

At this time there is insufficient evidence to draw firm conclusions regarding the safety and efficacy of Luxturna for the treatment of RPE65-mediated retinal dystrophies. There are multiple published reports of very small phase I/II trials, but only a single published phase III trial: 20 participants in this trial received treatment with Luxturna. The primary outcome measure in this trial is the multi-luminance mobility test (MLMT), a novel functional vision test that has not been used as an efficacy endpoint in any other clinical studies. Although treated participants demonstrated improvements in mobility and light sensitivity compared with untreated participants, there was no statistically significant improvement in visual acuity in the intention-to-treat population.

The United Kingdom's National Institute for Health and Care Excellence (NICE) published guidance for Luxturna 10/9/2019: “Voretigene neparvovec is recommended, within its marketing authorization, as an option for treating RPE65-mediated retinal dystrophies in people with vision loss caused by inherited retinal dystrophy from confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.” (https://www.nice.org.uk/guidance/hst11)

There is no available long-term follow-up data demonstrating durability of responses to Luxturna; further study is needed to validate the findings of the phase III trial and to confirm long-term benefit.

CODES:

Important note:

CODES: Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.

CPT Codes:	J3398
CPT Not Covered:	
ICD10 codes:	H35.50 Unspecified hereditary retinal dystrophy
ICD10 Not covered:	

CMS: Palmetto GBA LCD L37863 and LCA A56419

POLICY HISTORY:

Status	Date	Action
New	06/26/2018	New policy
Reviewed	02/26/2019	Code update
Reviewed	04/22/2020	Coverage criteria delineated
Updated	04/22/2021	Updated criteria applied by line of business
Reviewed	04/21/2022	Medicare instructions added

Reviewed	04/27/2023	No changes
Updated	09/28/2023	Updated Medicare and Medicaid instructions

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. FDA Label at: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM589541.pdf
2. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017 Aug 26;390(10097):849-860. doi: 10.1016/S0140-6736(17)31868-8. Epub 2017 Jul 14. PMID: 28712537
3. Bennett J, Wellman J, Marshall KA, et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: A follow-on phase 1 trial. Lancet. 2016;388(10045):661-672
4. Russell S, Bennett J, Wellman JA, et.al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017 Aug 26;390(10097):849-860. doi: 10.1016/S0140-6736(17)31868-8. Epub 2017 Jul 14
5. Maguire A, et.al. Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in RPE65 Mutation-Associated Inherited Retinal Dystrophy. Ophthalmology 2019;126:1273-1285