Luxturna® (Voretigene Neparvovec-Rzyl)

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Coverage Rationale

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Luxturna is proven and/or medically necessary for the treatment of inherited retinal dystrophies (IRD) caused by mutations in the retinal pigment epithelium-specific protein 65kDa (RPE65) gene in patients who meet all of the following criteria:[1-2]

- Patient is greater than 12 months of age; **and**
- 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 documenting biallelic mutations of the RPE65 gene; **and**
- Sufficient viable retinal cells as determined by optical coherence tomography (OCT) confirming an area of retina within the posterior pole of > 100 µm thickness; **and**
- Prescribed and administered by ophthalmologist or retinal surgeon with experience providing sub-retinal injections; **and**
- Patient has not previously received Luxturna treatment in intended eye; **and**
- Authorization will be issued for no more than one treatment per lifetime per eye and for no longer than 45 days from approval

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

HCPCS Code*	Required Clinical Information
Luxturna® (Voretigene Neparvovec-Rzyl)	

J3398	Medical notes documenting **all** of the following:
	• Medication name and regimen
	• Treatment of Inherited Retinal Dystrophies (IRD) including the following information:
	  ○ The member has not previously been treated with RPE65 gene therapy in the intended eye
	  ○ The member has sufficient retinal cells determined by the optical coherence tomography (OCT)

HCPCS Code*	Required Clinical Information
Luxturna® (Voretigene Neparvovec-Rzyl)	
	○ The treatment will be administered by an ophthalmologist or retinal surgeon experienced in providing sub-retinal injections ○ Current age of the patient ○ Genetic testing results confirming biallelic mutation of RPE65 gene

*For code description, refer to the Applicable Codes section.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3398	Injection, voretigene neparvovec-rzyl, 1 billion vector genomes

Diagnosis Code	Description
H35.50	Unspecified hereditary retinal dystrophy
H35.52	Pigmentary retinal dystrophy
H35.54	Dystrophies primarily involving the retinal pigment epithelium

Background

Leber's congenital amaurosis (LCA) and autosomal recessive retinitis pigmentosa (RP) are a group of inherited, early-onset, severe retinal dystrophies that cause substantial sight impairment in childhood.[3-5] One of the causes of these conditions is mutations in the gene encoding RPE65 (retinal pigment epithelium–specific protein 65 kDa). Biallelic mutations in the RPE65 gene account for approximately 16% of cases of LCA and 2% of cases of recessive RP. The encoded retinoid isomerase converts all-trans retinyl esters to 11-cis retinal for the regeneration of visual pigment after exposure to light. RPE65 deficiency causes photoreceptor- cell dysfunction and impaired vision from birth. Severe dysfunction of rod photoreceptor cells, which are wholly reliant on retinal pigment epithelium–derived RPE65, causes severely impaired night vision. The function of cone photoreceptor cells, which mediate vision in daylight, is relatively preserved in childhood because cones have access to an alternative source of 11-cis retinal. However, progressive degeneration of both rod and cone photoreceptor cells, in association with local accumulation of toxic retinyl esters, results in severe sight impairment by early adulthood.

Augmentation of RPE65 in animal models of RPE65 deficiency can improve retinal and visual function, as assessed by means of electroretinography (ERG) and observation of vision-guided behavior, respectively. Since the target retinal cells are post mitotic cells, it is expected that a one-time administration of the gene product will provide benefit as long as the retina cells are viable. Gene therapy treatment does not produce new tissue so it is vital the patient have sufficient viable retinal cells prior to administration. This can be measured by optical coherence testing (OCT) documenting a retinal layer $\geq$ 100 µm thick.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Phase 1 trials, done at the Children's Hospital of Philadelphia, showed safe and stable improvement in retinal and visual function in all 12 participants.[2] These individuals received unilateral, subretinal injections of AAV2-hRPE65v2 (voretigene neparvovec) in their worse-seeing, non-preferred eye in a dose-escalation study, with doses from $1{\cdot}5 \times 10^{10}$ to $1{\cdot}5 \times 10^{11}$ vector genomes (vg). Most of these participants showed improved light sensitivity, navigational abilities, or visual acuity. A follow-on study, in which 11 of these 12 participants underwent injection of the contralateral eye at the dose of $1{\cdot}5 \times 10^{11}$ vg, demonstrated the safety of contralateral eye injection, as well as gains in visual and retinal function in the second eye. This improvement has remained durable over at least 3 years, with observation ongoing.

The efficacy of voretigene neparvovec in pediatric and adult patients with biallelic RPE65 mutation-associated retinal dystrophy was evaluated in an open-lable, two-center, randomized trial.[1-2] Of the 31 enrolled subjects, 21 subjects with confirmed biallelic RPE65 mutations were randomized in a 2:1 fashion to either the voretigene neparvovec group or control group and followed for one year. After completion of one year of observation, control subjects were allowed to crossover and receive voretigene neparvovec treatment. Enrollment criteria include the following: subjects had to be at least three years of age with confirmed biallelic RPE65 mutations, subjects had to have a visual acuity of worse than or equal to 20/60 (for both eyes) and/or visual field of less than 20 degrees in any meridian as measured by a GVF III4e isopter or equivalent (both eyes), subjects had to have sufficient viable retinal cells as determined by non-invasive means, such as OCT (defined as an area of retina within the posterior pole of > 100 microns thickness) or ophthalmoscopy, subjects had to have the ability to comprehend the MLMT, follow course instructions, and the capacity to successfully navigate the course, and subjects had to have a baseline score on the MLMT that would allow a measurable improvement to be observed. The pre-specified primary efficacy endpoint was the change from Baseline at Year 1 in multi-luminance mobility test (MLMT) performance using the bilateral testing condition of the intervention group compared to controls. A total of 29 subjects were randomized and received intervention, 20 to the intervention arm and 9 to control. Overall, 72% of all treated subjects (21 of 29) achieved the maximum possible MLMT improvement one-year post-administration, demonstrating significant improvement in functional vision at lower light levels. The benefits observed at one year in the original intervention group continued through at least two years post-administration, with observation ongoing.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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). Treatment with Luxturna is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation and Luxturna would potentially be diluted or lost during cell proliferation.[1]

References

1. Luxturna [package insert]. Philadelphia, PA; Spark Therapeutics, Inc.; May 2022.
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;390:849-60.
3. Cai X, et al. RPE65: Role in the visual cycle, human retinal disease, and gene therapy. Ophthalmic Genet. 2009;30(2):57.
4. Carvalho L, Vandeberghe LH. Promising and delivering gene therapies for vision loss. Vision Research. 2015; 111:124.
5. Bainbridge JWB, et al. Long-term effect of gene therapy on Leber's congenital amaurosis. N Engl J Med. 2015; 372:1887.

Policy History/Revision Information

Date	Summary of Changes
11/01/2024	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version 2023D0063I

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.