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Voretigene Neparvovec-rzyl (Luxturna)

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Last Review 04/30/2024
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Policy

Scope of Policy

This Clinical Policy Bulletin addresses voretigene neparvovec-rzyl (Luxturna) for commercial medical plans. For Medicare criteria, see Medicare Part B Criteria (https://www.aetna.com/health-care-professionals/medicare/part-b-step.html).

Note: Requires Precertification:

Precertification of voretigene neparvovec-rzyl (Luxturna) is required of all Aetna participating providers and members in applicable plan designs. For precertification of voretigene neparvovec-rzyl (Luxturna), call (866) 752-7021 or fax (888) 267-3277. For Statement of Medical Necessity (SMN) precertification forms, see Specialty Pharmacy Precertification (https://www.aetna.com/health-care-professionals/health-care-professional-forms.html).

Note: Unless member's health plan has elected not to require, gene and cellular therapies must be administered at an Aetna Institutes® Gene Based, Cellular and Other Innovative Therapy (GCIT®) Network. For voretigene neparvovec-rzyl (Luxturna), see Aetna Institutes® GCIT Designated Centers (https://www.aetna.com/health-care-professionals/utilization-management/drug-infusion-site-of-care-policy.html).

I. Criteria for Initial Approval

Aetna considers voretigene neparvovec-rzyl (Luxturna) medically necessary for a one-time administration per eye for treatment of biallelic RPE65 mutation-associated retinal dystrophy when all of the following criteria are met:

A. The member has bi-allelic pathogenic and/or likely pathogenic RPE65 mutations via genetic testing (single gene test or multi gene panel test if medically necessary); and
B. The RPE65 gene mutations classifications are based on the current American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the

interpretation of sequence variants; and

C. Pathogenic and/or likely pathogenic classification of the RPE65 mutations has been affirmed within the last 12 months; and
D. The member is at least 12 months of age but less than 65 years of age; and
E. The member has viable retinal cells in each eye to be treated as determined by optical coherence tomography (OCT) and/or ophthalmoscopy; and must have any of the following:

    1. An area of retina within the posterior pole of greater than 100 µm thickness shown on OCT; or
    2. Greater than or equal to 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or
    3. Remaining visual field within 30 degrees of fixation as measured by a III4e isopter or equivalent; and

F. The member has not received a previous treatment course of voretigene neparvovec-rzyl (Luxturna).

Aetna considers all other indications as experimental, investigational, or unproven.

II. **Continuation of Therapy**

See Experimental, Investigational, or Unproven section.

III. **Genetic Testing for RPE65 Variant**

Aetna considers genetic testing for the RPE65 variant medically necessary to confirm a diagnosis of biallelic RPE65 variant-associated retinal dystrophy when Luxturna is being considered as a treatment option.

Aetna considers genetic testing for the RPE65 variant experimental, investigational, or unproven for all other indications.

IV. **Subretinal Injection of voretigene neparvovec-rzyl (Luxturna)**

Aetna considers subretinal injection of voretigene neparvovec-rzyl (Luxturna) medically necessary for the treatment of biallelic RPE65 mutation-associated retinal dystrophy when criteria are met.

Dosage and Administration

Voretigene neparvovec-rzyl is available as Luxturna. Luxturna is a suspension for subretinal injection, supplied in a 0.5 mL extractable volume in a single-dose 2 mL vial for a single administration in one eye. The supplied concentration (5x1012vg/mL) requires a 1:10 dilution prior to administration. The diluent is supplied in two single-use 2-mL vials.

Biallelic RPE65 mutation-associated retinal dystrophy: the recommended dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL injected into each eye on separate days within a close interval, but no fewer than 6 days apart.

Recommend systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of Luxturna to each eye), and followed by a tapering dose during the next 10 days.

Source: Spark Therapeutics, 2022

Experimental, Investigational, or Unproven

Aetna considers repeat administration of Luxturna in the same eye experimental, investigational, or unproven because the effectiveness of this approach has not been established.

CPT Codes / HCPCS Codes / ICD-10 Codes

Other CPT codes related to the CPB:

Code	Code Description
0810T	Subretinal injection of a pharmacologic agent, including vitrectomy and 1 or more retinotomies
67028	Intravitreal injection of a pharmacologic agent (separate procedure)
67036	Virectomy, mechanical, pars plana approach
67039	with focal endolaser photoconagulation
67040	with endolaser panretinal photocoagulation
67041	with removal of preretinal cellular membrane (eg, macular pucker)
67042	with removal of internal limiting membrane of retina (eg, for repair of macular hole, diabetic macular edema), includes, if performed, intraocular tamponade (ie, air, gas or silicone oil)
67043	with removal of subretinal membrane (eg, choroidal neovascularization), includes, if performed, intraocular tamponade (ie, air, gas, or silicone oil) and laser photocoagulation
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
92134	Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; retina
92201	Ophthalmoscopy, extended; with retinal drawing and scleral depression of peripheral retinal disease (eg, for retinal tear, retinal detachment, retinal tumor) with interpretation and report, unilateral or bilateral
92202	with drawing of optic nerve or macula (eg, for glaucoma, macular pathology, tumor) with interpretation and report, unilateral or bilateral
HCPCS codes covered if selection criteria are met:	
J3398	Injection, voretigene neparvovec-rzyl, 1 billion vector genome
ICD-10 codes covered if selection criteria are met:	
H35.50	Unspecified hereditary retinal dystrophy [bi-allelic RPE65 mutation-associated retinal dystrophy]

Background

U.S. Food and Drug Administration (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).

Voretigene neparvovec-rzyl is available as Luxturna (Sparks Therapeutics, Inc.). Luxturna is an adeno-associated virus vector-based gene therapy which is designed to deliver a normal copy of the gene encoding the human retinal pigment epithelial 65 kDa protein (RPE65) to cells of the retina in persons with reduced or absent levels of biologically active RPE65. The RPE65 is produced in the retinal pigment epithelial (RPE) cells and converts all-trans-retinol to 11-cis-retinol, which subsequently forms the chomophore, 11-cis-retinal, during the visual (retinoid) cycle. The visual cycle is critical in phototransduction, which refers to the biological conversion of a photon of light into an electrical signal in the retina. Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 isomerohydrolase activity, blocking the visual cycle and resulting in impairment of vision. Injection of Luxturna into the subretinal space results in transduction of some retinal pigment epithelial cells with a cDNA encoding normal human RPE65 protein, thus providing the potential to restore the visual cycle. (Sparks Therapeutics, 2019).

Luxturna carries the following warnings and precautions:

- Endophthalmitis
- Permanent decline in visual acuity
- Retinal abnormalities
- Increased intraocular pressure
- Expansion of intraocular air bubbles: Air travel and/or scuba diving is not recommended until any intraocular air bubbles have been absorbed.
- Cataract: Subretinal injection may result in cataract formation or increase in the rate of cataract progression.

In addition, the FDA-approved label for Luxturna states that "use in infants under 12 months of age is not recommended because of potential dilution or loss of Luxturna after administration due to the active retinal cells proliferation occurring in this age group". The most common adverse reactions (incidence 5% or more) in the clinical trials were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

According to the Prescribing Information (Spark Therapeutics, 2019), Luxturna for subretinal injection occurs after completing a vitrectomy. The subretinal injection cannula can be introduced via pars plana. Thus, the subretinal injection of Luxturna requires a pars plana vitrectomy.

Inherited Retinal Dypstrophies

Inherited retinal diseases (IRD), also known as inherited retinal dystrophies, are a group of rare blinding conditions caused by 1 of more than 220 different genes; RPE65-related IRD are rare and are caused by mutations in the RPE65 gene. In the United States, about 1,000 to 2,000 individuals are afflicted with bi-allelic (affecting both copies of a specific gene [on the paternal and maternal chromosomes]) RPE65 mutation-associated IRD. The RPE65 gene codes for the RPE-specific 65 kDa protein that is needed for the rods and cones to provide normal vision. Mutations in the RPE65 gene result in reduced or absent levels of RPE65 activity, blocking the visual cycle and leading to impaired vision. There are several types of RPE65-related IRDs. The most common are Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP). Individuals with IRD due to bi-allelic RPE65 gene mutations often experience nyctalopia (night blindness) due to decreased light sensitivity in childhood or early adulthood and nystagmus (involuntary back-and-forth eye

movements). As the disease progresses, individuals may experience loss in their peripheral vision, develope tunnel vision, and eventually, they may lose their central vision as well, resulting in total blindness. Independent navigation becomes severely limited, and vision-dependent activities of daily living are impaired. Current investigational therapies for RP include gene therapy, cell therapy, and retinal prostheses. Gene therapy has the potential to achieve definitive treatment by replacing or silencing a causative gene. Recently, several clinical trials recently showed significant efficacy of voretigene neparvovec, an ocular gene therapy, for RPE65-mediated IRD. Voretigene neparvovec works by delivering a normal copy of the RPE65 gene directly to retinal cells, which then produce the normal protein that converts light to an electrical signal in the retina to restore patients' vision loss. Voretigene neparvovec uses a naturally occurring adeno-associated virus (AAV), which has been modified using recombinant DNA techniques, as a vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision.

Bennett and co-workers (2016) noted that safety and efficacy have been shown in a phase-I, dose-escalation clinical trial involving a unilateral sub-retinal injection of a recombinant AAV vector containing the RPE65 gene (AAV2-hRPE65v2) in individuals with iIRD caused by RPE65 mutations. This finding, along with the bilateral nature of the disease and intended use in treatment, prompted these researchers to determine the safety of administration of AAV2-hRPE65v2 to the contralateral eye in patients enrolled in the phase-I study. In this follow-on study, 1 dose of AAV2-hRPE65v2 (1.5×10^{11} vector genomes) in a total volume of 300 µL was sub-retinally injected into the contralateral, previously un-injected, eyes of 11 children and adults (aged 11 to 46 years at 2nd administration) with IRD caused by RPE65 mutations, 1.71 to 4.58 years after the initial sub-retinal injection. These investigators evaluated safety, immune response, retinal and visual function, functional vision, and activation of the visual cortex from baseline until 3-year follow-up, with observations ongoing. No adverse events (AEs) related to the AAV were reported, and those related to the procedure were mostly mild including dellen (thinning of the corneal stroma) formation in 3 patients and cataracts in 2. One patient developed bacterial endophthalmitis and was excluded from analyses. These researchers noted improvements in efficacy outcomes in most patients without significant immunogenicity. Compared with baseline, pooled analysis of 10 participants showed improvements in mean mobility and full-field light sensitivity in the injected eye by day 30 that persisted to year 3 (mobility $p = 0.0003$, white light full-field sensitivity $p < 0.0001$), but no significant change was seen in the previously injected eyes over the same time period (mobility $p = 0.7398$, white light full-field sensitivity $p = 0.6709$). Changes in visual acuity (VA) from baseline to year 3 were non-significant in pooled analysis in the second eyes or the previously injected eyes ($p > 0.49$ for all time-points compared with baseline). The authors concluded that AAV2-hRPE65v2 is the first successful gene therapy administered to the contralateral eye.

In a non-randomized, multi-center, clinical trial, Weleber and associates (2016) provided initial assessment of the safety of a recombinant AAV vector expressing RPE65 (rAAV2-CB-hRPE65) in adults and children with retinal degeneration caused by RPE65 mutations. A total of 8 adults and 4 children, aged 6 to 39 years, with LCA or severe early-childhood-onset retinal degeneration (SECORD) were included in this analysis. Patients received a sub-retinal injection of rAAV2-CB-hRPE65 in the poorer-seeing eye, at either of 2 dose levels, and were followed-up for 2 years after treatment. The primary safety measures were ocular and non-ocular AEs. Exploratory efficacy measures included changes in best-corrected VA (BCVA), static perimetry central 30° visual field hill of vision (V30) and total visual field hill of vision (VTOT), kinetic perimetry visual field area, and responses to a quality-of-life (QOL) questionnaire. All patients tolerated sub-retinal injections and there were no treatment-related serious AEs. Common AEs were those associated with the surgical procedure and included subconjunctival hemorrhage in 8 patients and ocular hyperemia in 5 patients . In the treated eye, BCVA increased in 5 patients,

V30 increased in 6 patients, VTOT increased in 5 patients, and kinetic visual field area improved in 3 patients. One subject showed a decrease in BCVA and 2 patients showed a decrease in kinetic visual field area. The authors concluded that treatment with rAAV2-CB-hRPE65 was not associated with serious AEs; and improvement in 1 or more measures of visual function was observed in 9 of 12 patients. The greatest improvements in VA were observed in younger patients with better baseline VA. They stated that evaluation of more patients and a longer duration of follow-up are needed to determine the rate of uncommon or rare side effects or safety concerns.

In a randomized, controlled, open-label, phase-III clinical trial, Russell and colleagues (2017) evaluated the safety and efficacy of voretigene neparvovec in participants whose IRD would otherwise progress to complete blindness. This study was carried out at 2 sites in the United States; individuals aged 3 years or older with, in each eye, BCVA of 20/60 or worse, or visual field less than 20 degrees in any meridian, or both, with confirmed genetic diagnosis of bi-allelic RPE65 mutations, sufficient viable retina, and ability to perform standardized multi-luminance mobility testing (MLMT) within the luminance range evaluated, were eligible. Participants were randomly assigned (2:1) to intervention or control using a permuted block design, stratified by age (less than 10 years; and greater than or equal to 10 years) and baseline mobility testing passing level (pass at greater than or equal to 125 lux versus less than 125 lux). Graders assessing primary outcome were masked to treatment group. Intervention was bilateral, sub-retinal injection of 1.5×10^{11} vector genomes of voretigene neparvovec in 0.3 ml total volume. The primary efficacy end-point was 1-year change in MLMT performance, measuring functional vision at specified light levels. The intention-to-treat (ITT) and modified ITT (mITT) populations were included in primary and safety analyses. Between November 15, 2012 and November 21, 2013, a total of 31 individuals were enrolled and randomly assigned to intervention (n = 21) or control (n = 10); 1 subject from each group withdrew after consent, before intervention, leaving an mITT population of 20 intervention and 9 control subjects. At 1 year, mean bilateral MLMT change score was 1.8 (SD 1.1) light levels in the intervention group versus 0.2 (1.0) in the control group (difference of 1.6, 95 % confidence interval [CI]: 0.72 to 2.41, p = 0.0013); 13 (65 %) of 20 intervention subjects, but no control subjects, passed MLMT at the lowest luminance level tested (1 lux), demonstrating maximum possible improvement. No product-related serious AEs or deleterious immune responses occurred. Two intervention participants, one with a pre-existing complex seizure disorder and another who experienced oral surgery complications, had serious AEs unrelated to study participation. Most ocular events were mild in severity. The authors concluded that voretigene neparvovec gene therapy improved functional vision in RPE65-mediated IRD previously medically untreatable.

Dias and associates (2017) noted that RP is a hereditary retinopathy that affects about 2.5 million people worldwide. It is characterized with progressive loss of rods and cones and causes severe visual dysfunction and eventual blindness. In addition to more than 3,000 genetic mutations from about 70 genes, a wide genetic overlap with other types of IRD has been reported with RP. This diversity of genetic pathophysiology makes treatment extremely challenging. These investigators stated that voretigene neparvovec has the potential to achieve definitive treatment by replacing or silencing a causative gene. They noted that voretigene neparvovec is about to be approved as the first ocular gene therapy. Despite current limitations such as limited target genes and indicated patients, modest efficacy, and the invasive administration method, development in gene editing technology and novel gene delivery carriers make gene therapy a promising therapeutic modality for RP and other IRD in the future.

On December 19, 2017, the Food and Drug Administration (FDA) approved voretigene neparvovec-rzyl (Luxturna) for the treatment of children and adult patients with confirmed bi-allelic RPE65 mutation-associated retinal dystrophy that

leads to vision loss and may cause complete blindness. To further evaluate the long-term safety, the manufacturer plans to conduct a post-marketing observational study involving patients treated with Luxturna.

A phase-III clinical trial on "Gene therapy intervention by subretinal administration of AAV2-hRPE65v2 in subjects with Leber congenital amaurosis" provides the following inclusion criteria:

- Willingness to adhere to protocol and long-term follow-up as evidenced by written informed consent or parental permission and subject assent (where applicable).
- Diagnosis of LCA due to RPE65 mutations; molecular diagnosis is to be performed, or confirmed, by a CLIA-approved laboratory.
- Age 3 years old or older.
- Visual acuity worse than 20/60 (both eyes) and/or visual field less than 20 degrees in any meridian as measured by a III4e isopter or equivalent (both eyes).
- Sufficient viable retinal cells as determined by non-invasive means, such as optical coherence tomography (OCT) and/or ophthalmoscopy. Must have either:
    - an area of retina within the posterior pole of greater than 100 µm thickness shown on OCT;
    - greater than or equal to 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or
    - remaining visual field within 30 degrees of fixation as measured by a III4e isopter or equivalent.
- Subjects must be evaluable on mobility testing (the primary efficacy end-point) to be eligible for the study. Evaluable is defined as:
    - The ability to perform mobility testing within the luminance range evaluated in the study. Individuals must receive an accuracy score of less than or equal to 1 during screening mobility testing at 400 lux or less to be eligible; individuals with an accuracy score of greater than 1 on all screening mobility test runs at 400 lux, or those who refuse to perform mobility testing at screening, will be excluded;
    - The inability to pass mobility testing at 1 lux. Individuals must fail screening mobility testing at 1 lux to be eligible; individuals that pass one or more screening mobility test runs at 1 lux will be excluded.

ACMG Standards and Guidelines

The American College of Medical Genetics and Genomics (ACMG) is a specialty society that develop and sustain genetic and genomic initiatives in clinical and laboratory practice, education, and advocacy. The ACMG have created a standards and guidelines report for the classification and interpretation of sequence variants, which includes defined terms for variant classification guidance. For instance, the term "mutation" is defined as a permanent change in the nucleotide sequence, whereas polymorphism is defined as a variant with a frequency above 1%. ACMG notes these terms often lead to confusion because of incorrect assumptions of pathogenic and benign effects. Therefore, ACMG recommends replacing those terms for the use of specific standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign". Furthermore, the recommendations describe a process for classifying variants into these five categories based on criteria using typical types of variant evidence (e.g., population data, computational data, functional data, segregation data). These recommendations primarily apply to the breadth of genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Due to the increased complexity of analysis and interpretation of clinical genetic testing described in the ACMG Standards and Guidelines report, the ACMG strongly recommends that clinical molecular genetic testing be performed in a Clinical Laboratory Improvement Amendments–approved laboratory, with results

interpreted by a board-certified clinical molecular geneticist or molecular genetic pathologist or the equivalent (Richards et al, 2015). See ACMG Standards and Guidelines for the Interpretation of Sequence Variants (https://www.acmg.net/docs/standards_guidelines_for_the_interpretation_of_sequence_variants.pdf).

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The above policy is based on the following references:

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