

## DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

## OVERVIEW

**This policy covers Luxturna (voretigene neparvovec-rzyl) for the treatment of retinal dystrophy due to biallelic mutations in the RPE65 gene.**

**Inherited retinal diseases** (also known as inherited retinal dystrophies or IRD) are a set of rare diseases characterized by vision loss and ultimately blindness due to an inherited gene mutation affecting the retina. More than 260 genes have been linked to IRD (Duncan et al. 2018). In children and young adults, IRD is a leading cause of blindness and impaired visual acuity. IRD due to biallelic mutations in the RPE65 gene is the most severe form of IRD. The RPE65 gene codes for the enzyme, retinoid isomerohydrolase, which is essential for phototransduction of light at the retina. Mutations in the RPE65 gene disrupt phototransduction and lead to toxic accumulation of visual cycle metabolites. These toxins damage the retina and photoreceptors within, leading to almost complete blindness in most cases. Luxturna gene therapy adds missing DNA instructions to make the enzyme, retinoid isomerohydrolase, thereby restoring the visual cycle and improving vision.

Prior to the approval of Luxturna, there were no pharmacologic treatments for IRD. The standard of care included supportive services such as training for low-vision and the use of visual aids or mobility devices. Current treatment options include refractive error correction and the use of low-vision aids. RPE65-related inherited retinal dystrophy (RPE65-IRD) is expected to affect 1,000 to 2,000 persons in the United States (Lloyd et al. 2019).

**Luxturna (voretigene neparvovec-rzyl)** delivers a normal copy of the RPE65 gene via adeno-associated virus, serotype 2 (AAV2), to retinal cells without a normal RPE65 gene. The protein product of the RPE65 gene then transforms light into an electrical signal in the retina allowing for vision. Luxturna gene therapy does not fix or remove the defective gene, it simply adds a normal copy of the gene into retinal cells.

Luxturna is the first FDA-approved gene therapy to treat IRD caused by biallelic RPE65 gene mutations. It is intended to be a one-time gene therapy delivered to the retinal pigment epithelium via subretinal injection under general anesthesia. Luxturna was approved by the FDA based on one open-label, dose-exploration Phase 1 safety study (n=12) and one phase 3, open-label, randomized controlled trial (RCT) of efficacy and safety. The study enrolled a total of 31 participants with biallelic RPE65 mutation-associated retinal dystrophy and sufficient viable retinal cells, including both pediatric and adult participants (Russell et al. 2017).

## COVERAGE POLICY

Luxturna (voretigene neparvovec-rzyl) for the treatment of retinal dystrophy **may be considered medically necessary** when **ALL** of the following clinical criteria are met:

1. Diagnosis of confirmed \*biallelic RPE65 mutation-associated retinal dystrophy via genetic testing

*\*Biallelic mutation is a mutation on both copies of the RPE65 gene (affecting the function of both copies) and cause LCA2, EOSRD, SECORD, and RP20.*

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*Informational Note: Luxturna has only been studied for IRDs due to biallelic RPE65 mutations. There is no evidence Luxturna could work for IRDs due to other mutations. Spark Therapeutics may offer access to genetic testing designed to identify biallelic RPE65 mutations. For more information about the program and eligibility requirements, visit [www.luxturna.com](http://www.luxturna.com).*

2. Member is greater than 1 years of age but less than 65 years of age at the time of therapy initiation
3. Presence of **viable retinal cells** as evidenced by optical coherence tomography (OCT) imaging and/or ophthalmoscopy documented by **ONE or more** of the following:
  - a. An area of retina within the posterior pole of >100 µm thickness
  - b. Greater than or equal to 3-disc areas of retina without atrophy or pigmentary degeneration within the posterior pole
  - c. Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent

*Informational Note: 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 OCT. Patients who did not show any viable retinal cells were excluded from the clinical studies of Luxturna and may not benefit from treatment based on its mechanism of action.*

3. Luxturna treatment requested for **ONE** of the following. Documentation required:
  - a. Left eye
  - b. Right eye
  - c. Both eyes

**NOTE:** If request is authorized for BOTH eyes, Luxturna must be administered to each eye on separate days at least 6 days apart

4. Member does not have other pre-existing eye conditions or complicating systemic diseases that is expected to eventually lead to irreversible vision loss and prevent the full benefit of the requested Luxturna treatment
5. Member has NOT previously been: [ALL]
  - a. Enrolled in clinical trials of gene therapy for retinal dystrophy RPE65 mutations
  - b. Treated with gene therapy for retinal dystrophy in the requested/intended treatment eye(s); Previous subretinal administration of a gene therapy vector, or voretigene into the operative eye
  - c. Prescribed for use in combination with other gene therapy in the requested/intended treatment eye(s)

*Informational Note: Luxturna has not been studied after or in combination with other gene therapies.*

6. Member has NOT received intraocular surgery within prior 6 months

### **CONTINUATION OF THERAPY**

Coverage of Luxturna is limited to a single treatment per eye and may not be authorized for re-treatment.

**Experimental and Investigational:** Re-treatment and repeated doses with Luxturna in the same eye are not supported by compendia and considered experimental and investigational. The safety and efficacy of repeat injections in the same eye have not been evaluated in clinical studies. In clinical studies, patients received treatment in each eye once. Additional studies and clinical experience with Luxturna are required to determine the role of retreatment and to identify safety issues with repeat dosing.

### **LIMITATIONS AND EXCLUSIONS**

The following are **considered contraindications/exclusions/discontinuations** based on insufficient evidence:

1. Hypersensitivity to voretigene or any component of the formulation
2. Previous treatment with Luxturna or other gene therapy or in combination with other gene therapy in the requested/intended treatment eye(s)
3. Pre-existing eye conditions or complicating systemic diseases that would eventually lead to irreversible vision loss and prevent full benefit of requested Luxturna therapy

*Informational Note: Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can*

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*alter ocular function (e.g., malignancies whose treatment could affect CNS function such as radiotherapy of the orbit; leukemia with central nervous system/optic nerve involvement)*

4. Immunodeficiency (acquired or congenital) due to susceptibility to opportunistic infection (e.g., cytomegalovirus retinitis)
5. Intraocular surgery within prior 6 months
6. Pregnancy or breastfeeding

*Informational Note: Adequate and well-controlled studies of Luxturna have not been conducted in pregnant women. There is no information on the presence of Luxturna in human milk, the effects on the breastfed infant, or the effects on milk production.*

The following are considered **experimental, investigational, or unproven** based on insufficient evidence:

1. Any indications other than those listed above
2. Repeat treatment in the same eye is not supported by compendia and not considered not medically necessary

**DURATION OF APPROVAL:** 4 weeks (ONE dose per eye for lifetime)

**PRESCRIBER REQUIREMENTS:** Prescribed by, or in consultation with, an ophthalmologist or retinal surgeon provider at a center of excellence who is trained in, and follows administration and treatment protocols, for Luxturna. Submit consultation notes if applicable.

*Clinical Rationale: Luxturna was studied in an open-label phase 3 RCT. Individuals aged 3 years or older with a confirmed genetic diagnosis of biallelic RPE65 gene mutations were eligible for enrollment (n= 31). Phase III Trial of Luxturna (Russell et al. 2017). 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. Clinical studies for this indication did not include patients ages 65 year and over. The safety and effectiveness of Luxturna have not been established in geriatric patients.*

#### **DOSING CONSIDERATIONS:**

1. Usual recommended dose:  $1.5 \times 10^{11}$  vector genomes (vg) administered via 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
2. If request is authorized for BOTH eyes, Luxturna must be administered to each eye on separate days at least 6 days apart

#### **QUANTITY LIMITATIONS**

1. ONE (1) injection ( $1.5 \times 10^{11}$  vg) per eye
2. ONE single-dose vial per eye per member per lifetime

#### **ADMINISTRATION**

1. Gene therapy is provided at highly specialized facilities with an active ophthalmology practice that treats patients with retinal dystrophies\
2. Use of Luxturna is limited to medical centers with retina specialists with expertise in inherited retinal disorders, vitreoretinal surgery expertise, and pharmacies adequately trained to handle the product
3. Refer to MHI Policy & Procedure: Specialty Medication Administration Site of Care Policy: MHI Pharm 11

**DOCUMENTATION REQUIREMENTS.** Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

**SUMMARY OF MEDICAL EVIDENCE**

The FDA approval of Luxturna was based on one open-label, dose-exploration Phase 1 safety study (n=12) and one open-label phase 3 RCT efficacy and safety study (n=31) in pediatric and adult participants (range 4 to 44 years) with biallelic RPE65 mutation-associated retinal dystrophy and sufficient viable retinal cells.

**Phase 1 Trial** (NCT01208389 & NCT00516477). Open-label, dose-escalation study. These studies allowed for dose selection, established a safety profile, and created clear-cut endpoints for the phase 3 trial.

Bennett et al. (2016) assessed the safety and efficacy of administering the treatments in the contralateral eye in a follow-up to the initial study (NCT00516477). A total of 11 of the 12 original participants received an injection in the contralateral, untreated eye and were evaluated on a regular basis for 3 years. The age range in this study was 11-46 years of age. An individual with glaucoma in the uninjected eye could not be included in this follow-up study. One individual developed bacterial endophthalmitis following the injection. The remaining adverse effects related to the procedure included dellen formation (n=2) and cataracts (n=1), all of which were successfully treated. For the majority of outcomes, results for the second injected eye were compared with results over the same follow-up period for the initial injected eye.

In a pooled analysis, results from full-field light sensitivity threshold (FST) testing showed robust improvements in both rod and cone function in the contralateral eyes by day 30 through year 3. A pooled analysis also did not show any significant changes in visual acuity from baseline through year 3 in either eye. There were reported significant improvements in mobility testing and pupillary light reflex testing results which lasted through year 3.

**Phase 3 Trial** (NCT00999609). FDA approval of Luxturna was primarily based on the results of an open-label phase 3 RCT of 31 patients ages 3 or older with biallelic RPE65 variants (Russell et al., 2017). Enrollment criteria include the following: subjects had to be at least 3 years of age with a confirmed genetic diagnosis of 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. Subjects were excluded if they had participated in previous gene therapy or invitational drug study, had intraocular surgery within the prior 6 months, used high-dose (7500 retinol equivalent units [or >3300 IU] per day of vitamin A) retinoid compounds in the past 18 months, had known hypersensitivity to medications planned for use in the peri-operative period, or had ocular or systemic conditions that would interfere with study interpretation.

- Voretigene (n=20) was injected in the first eye and then injected on day 6 to 18 in the second eye. A control group (n=9) did not receive therapy for 1 year at which time they could cross over and receive recombinant AAV voretigene therapy. *One patient in each treatment group withdrew before the year 1 visit; neither received voretigene.*
- The primary efficacy endpoint was the change from baseline to 1 year in the score of the MLMT, an assessment of functional vision at specified light levels: voretigene had an average of 1.9 to 2.1 improvement in MLMT scores while placebo had an average of 0.1 to 0.2 score improvement depending on the eye. Differences between voretigene and controls scores were statistically significant. Improvements in MLMT scores for voretigene was stable throughout year 1. Mean FST scores in the intervention group improved by 30 days following intervention and remained stable at 1 year. There was no meaningful change in FST scores in the control group at 1 year. The best-corrected visual acuity BCVA scores in the intervention group did show an insignificant numerical improvement over the control group.
- Secondary efficacy endpoints also included FST testing and best-corrected visual acuity (BCVA), each averaged over both eyes: voretigene had a greater than 2 log unit improvement by day 30 in light sensitivity that remained stable over 1 year. The control group had no meaningful change in this measure over 1 year. The difference between voretigene and control of -2.11 (-3.19 to -1.04) was statistically significant (p=0.0004).
- For another secondary endpoint of BCVA averaged over both eyes, voretigene had a mean improvement of 8.1 letters on the eye chart while control had a mean gain of 1.6 letters which was not statistically significant.



The most common treatment-related ocular adverse events (AEs) included elevated intraocular pressure, cataract and eye inflammation and were considered mild or moderate. There were no major product-related AEs or adverse immunological reactions. One individual in the intervention group experienced severe loss of visual acuity in the first eye, although the individual did not report a change in vision. The authors noted the loss may be attributable to foveal thinning following subretinal injection, although the analysis was unclear. In a randomized trial of adult and pediatric patients with biallelic RPE65 mutation-associated retinal dystrophy, voretigene significantly improved functional vision compared to the placebo after 1 year, and this effect was maintained for 2 years. Luxturna treatment improved light sensitivity, visual fields, and navigation abilities in patients who had no other therapeutic options.

Maguire et al. (2021) published phase 3 results at years 3 and 4 from trial NCT04516369. The Durability of voretigene treatment was assessed per the original study protocol. Improvements in ambulatory navigation, light sensitivity and visual fields were maintained up to 3-4 years. No new safety signals emerged during this follow-up period.

Leroy et al. (2023) reported outcomes of Luxturna therapy were sustained for up to 7.5 years in the phase 1 study. The multi-luminance mobility test results were maintained for 5 years in the phase 3 study.

Fischer et al. (2024) reported data from the multi-national PERCEIVE study which is a registry based study evaluating real world safety and effectiveness of voretigene. Data was gathered from 103 patients treated with voretigene. The age range in the study was 2 – 51 years of age. The safety & effectiveness of voretigene including FST improvement were consistent with initial clinical trial data. FST (Full field Stimulus Threshold) is measured in decibels. In FST a negative dB score means the patient has a higher sensitivity to light flashes compared to a reference level or baseline level. In other words, a negative dB means the study participant can detect light flashes that are fainter than at baseline. The mean FST was -4.56 at baseline and -16.59 and -18.24 at months 1 and 6 post voretigene treatment.

Long-term follow-up data indicating durability of responses to voretigene injection are lacking presently. A long-term follow-up study in patients who received voretigene is ongoing; this observational study will follow patients for up to 15 years after treatment (NCT03602820). Another observational study post voretigene therapy NCT03597399 is ongoing but results have not been reported as of July 2024.

**Systematic Reviews/Meta-Analyses.** No systematic reviews or meta-analyses pertaining to voretigene for the treatment of IRD were found during the literature search.

### **National and Specialty Organizations**

**The American Academy of Ophthalmology (AAO)** (2022) issued guidelines for the clinical assessment of patients with inherited retinal disease. These guidelines focus on the diagnosis and screening of IRDs. Genetic testing and screening were particularly emphasized; voretigene was noted as a treatment option for RPE65 related IRD. The AAO recommends genetic testing be ordered at the initial visit for individuals with a suspected IRD since the causative mutation can be identified in up to 60-80% of affected individuals, which can guide treatment decisions (AAO 2016).

**The National Institute for Health and Care Excellence (NICE)** (2019) recommended Luxturna for the treatment of RPE65-mediated IRD in people with vision loss and sufficient viable retinal cells.

## **SUPPLEMENTAL INFORMATION**

*Adeno-associated viruses (AAV)* are frequently utilized due to their unique biology and simple structure. These viruses are in the parvovirus family and are dependent on co-infection 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 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.

*Biallelic Mutation* is a mutation in both copies of a particular gene that affects the function of both copies. *Biallelic RPE65 mutation-associated retinal dystrophy* is a mutation on both copies of the RPE65 gene (affecting the function

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of both copies) and cause Leber's congenital amaurosis 2 (LCA2), Early Onset Severe Retinal Dystrophy (EOSRD) and Severe Early Childhood-onset Retinal Dystrophy (SECORD), Retinitis Pigmentosa type 20 (RP20).

*Multi-Luminance Mobility Testing (MLMT)* was developed to study voretigene. It is a standardized, lab-based test that simulates everyday walking environments. Participants were observed while navigating a course with obstacles of varying height under different levels of illumination. MLMT assesses the ability to navigate an obstacle course at varying light levels and was designed to be a functional measure that would best capture the impact of treatment. The MLMT is a 5 ft. by 10 ft. obstacle course with 12 distinct but standardized layouts, each with the same number of arrows, turns, and hazards (designed for a visual acuity of 20/200 on the Snellen chart). The primary efficacy endpoint for the Phase III trial was change in bilateral MLMT performance. Participants were started at the lowest light levels (lux), moving higher until they passed. Individuals without vision impairment pass this test at the lowest light level (1 lux) 100% of the time.

*RPE65 (retinal pigment epithelium-specific protein 65-kD)* 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. Retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA) both have subtypes related to pathogenic variants in RPE65.

## CODING & BILLING INFORMATION

### CPT (Current Procedural Terminology) Codes

| Code  | Description  |
|-------|--|
| 67036 | Vitrectomy, mechanical, pars plana approach  |
| 67299 | Unlisted procedure, posterior segment  |
| 0810T | Subretinal injection of a pharmacologic agent, including vitrectomy and 1 or more retinotomies |

### HCPCS (Healthcare Common Procedure Coding System) Code

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

**AVAILABLE DOSAGE FORMS:** A suspension supplied in a 0.5 mL extractable volume in a 2 mL single-dose vial; the supplied concentration ( $5 \times 10^{12}$  vg/mL) requires a 1:10 dilution prior to administration.

**CODING DISCLAIMER.** Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

## APPROVAL HISTORY

|            |   |
|------------|---|
| 08/14/2024 | Policy reviewed, changes to criteria include minimum member age now 1 year. IRO Peer Review on August 7, 2024 by a practicing, board-certified physician with a specialty in ophthalmology  |
| 08/09/2023 | Policy reviewed. No coverage criteria changes. Minor revisions, including clarification and addition of language, however no change to content.   |
| 08/10/2022 | Policy reviewed. No coverage criteria changes. Minor revisions, including clarification and addition of language, however no change to intent.  |
| 08/11/2021 | Policy revised. IRO Peer Review. 7/14/2021. Practicing Physician. Board certified in Ophthalmology, Surgery Vitreoretina. Minor revisions, including clarification and addition of verbiage to criteria, however no change to intent in coverage criteria.  |
| Q3 2020    | Policy reviewed. No coverage criteria changes. Minor revisions, including clarification and addition of language, however no change to intent.  |
| Q4 2019    | Policy revised. IRO Peer Review. 9/9/2019. Practicing Physician. Board certified in Ophthalmology, Surgery Vitreoretina. Notable revisions include: <ul style="list-style-type: none"><li>Revised prescriber specialty criterion for clarity (added: 'at a center of excellence who is trained for and following administration and treatment protocols for voretigene neparvovec');</li><li>Added criterion: Member does not have other pre-existing eye conditions or complicating systemic diseases that is expected to eventually lead to irreversible vision loss and prevent the full benefit of the requested Luxturna treatment;</li><li>Added criterion: Luxturna treatment requested for: Left eye, OR Right eye, OR Both eyes AND If request is for BOTH eyes:</li></ul> |

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If both eyes are to be treated, Luxturna (voretigene neparvovec) must be administered to each eye on separate days at least 6 days apart.

- Revised the first criteria under #4 from: Member has not previously been treated with Luxturna (Voretigene neparvovec-rzyl) or other gene therapy or in combination with other gene therapy in the requested/intended treatment eye(s)  
*To: Member has not previously been: Enrolled in clinical trials of gene therapy for retinal dystrophy RPE65 mutations, and treated with gene therapy for retinal dystrophy in the requested/intended treatment eye(s), and Prescribed for use in combination with other gene therapy in the requested/intended treatment eye(s).*

06/14/2018

Policy developed. IRO Peer Review: 2/5/2018. Practicing Physician. Board certified in Retinal Surgery.

## REFERENCES

- American Academy of Ophthalmology. Recommendations on clinical assessment of patients with inherited retinal degenerations. Published June 2016. Updated October 6, 2022. Accessed July 2024. <https://www.aao.org/education/clinical-statement/guidelines-on-clinical-assessment-of-patients-with>.
- American Society of Gene and Cell Therapy. Addressing the value of gene therapy and enhancing patient access to transformative treatments. Molecular Therapy. 2018;26(12). Accessed July 2022. [https://www.asgct.org/ASGCT/media/about/ValueAccessWhitePaper\\_MTUpdate2-8.pdf](https://www.asgct.org/ASGCT/media/about/ValueAccessWhitePaper_MTUpdate2-8.pdf)
- 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 Aug 13;388(10045):661-72. doi: 10.1016/S0140-6736(16)30371-3.
- Campa C, Gallenga CE, Bolletta E, Perri P. The role of gene therapy in the treatment of retinal diseases: a review. Curr Gene Ther. 2017;17(3):194-213. doi: 10.2174/1566523217666171116170040. PMID 29149824.
- Centers for Medicare and Medicaid Services (CMS). Medicare coverage database (no National Coverage Determination identified). Accessed July 2024. <https://www.cms.gov/medicare-coverage-database/search.aspx>.
- Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. Published 2022. Accessed April 2022. <http://www.clinicalkey.com>.
- Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Available from Wolters Kluwer Health, Inc. Accessed April 2022. <https://www.wolterskluwer.com/>.
- Duncan JL, Pierce EA, Laster AM, et al. Inherited retinal degenerations: Current landscape and knowledge gaps. Transl Vis Sci Technol. 2018 Jul 18;7(4):6. doi: 10.1167/tvst.7.4.6.
- Fischer MD, Simonelli F, Sahni J, et al. Real-World Safety and Effectiveness of Voretigene Neparvovec: Results up to 2 Years from the Prospective, Registry-Based PERCEIVE Study. Biomolecules. 2024 Jan 17;14(1):122. doi: 10.3390/biom14010122. PMID: 38254722; PMCID: PMC10813228.
- Garg S. Retinitis pigmentosa: Treatment. Updated April 16, 2024. Accessed July 2024. [www.uptodate.com](http://www.uptodate.com).
- Garg S. Retinitis pigmentosa: Clinical presentation and diagnosis. Updated September 9, 2022. Accessed July 2024. [www.uptodate.com](http://www.uptodate.com).
- Hayes. Precision therapy assessment (Annual Review): Voretigene neparvovec-rzyl (Luxturna) for inherited retinal dystrophies. Published September 21, 2020. Updated June 12, 2023. Accessed July 2024.
- Institute for Clinical and Economic Review (ICER). Voretigene neparvovec for biallelic RPE65-mediated retinal disease: Effectiveness and value – final evidence report. Published February 14, 2018. Accessed July 2022. [https://icer.org/wp-content/uploads/2020/10/MWCEPAC\\_VORETIGENE\\_FINAL\\_EVIDENCE\\_REPORT\\_02142018.pdf](https://icer.org/wp-content/uploads/2020/10/MWCEPAC_VORETIGENE_FINAL_EVIDENCE_REPORT_02142018.pdf).
- Leroy BP, Fischer MD, Flannery JG, et al. Gene Therapy for Inherited Retinal Disease: Long-Term Durability of Effect. Ophthalmic Res. 2023;66(1):179-196. doi: 10.1159/000526317. Epub 2022 Sep 14. PMID: 36103843.
- Lloyd A, Piglowaska N, Ciulla T, et al. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. Br J Ophthalmol. 2019 Nov;103(11):1610-1614. doi: 10.1136/bjophthalmol-2018-313089. Accessed July 2022.
- Luxturna (voretigene neparvovec-rzyl) [prescribing information]. Philadelphia: Spark Therapeutics Inc; May 2022. <https://www.fda.gov/media/109906/download>.
- Maguire AM, Russell S, Chung DC, et al. Durability of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease: Phase 3 Results at 3 and 4 Years. Ophthalmology. 2021 Oct;128(10):1460-1468. doi: 10.1016/j.ophtha.2021.03.031. Epub 2021 Mar 30. PMID: 33798654.
- Maguire AM, Russell S, Wellman JA, et al. Efficacy, safety, and durability of voretigene neparvovec-rzyl in RPE65 mutation-associated inherited retinal dystrophy: Results of phase 1 and 3 trials. Ophthalmology. 2019 Sep;126(9):1273-1285. doi: 10.1016/j.ophtha.2019.06.017.
- National Institute for Health and Care Excellence (NICE). Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations (HST11). Published October 9, 2019. Accessed July 2024. <https://www.nice.org.uk/guidance/hst11>.
- 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.
- United States Food and Drug Administration (FDA). Cellular and gene therapy products: Luxturna (STN 125610). Updated June 9, 2022. Accessed July 2023. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna>.
- United States Food and Drug Administration (FDA). Biologics License Application (BLA) approval letter. Published December 19, 2017. Accessed June 2022. <https://www.fda.gov/media/109487/download?attachment>.
- United States Food and Drug Administration (FDA). FDA News Release. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. Published December 18, 2017. Accessed June 2022. <https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss>.
- United States Food and Drug Administration (FDA). BLA clinical review memorandum. Published December 16, 2017. Accessed June 2022. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna>.
- 4 United States Food and Drug Administration (FDA). FDA Advisory Committee briefing document: Spark Therapeutics, Inc. – Luxturna (voretigene neparvovec). Published October 12, 2017. Accessed June 2022. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna>.