Molina Clinical Policy
Luxturna (voretigene neparvovec-rzyl): Policy No. 318

Last Approval: 8/10/2022
Next Review Due By: August 2023

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

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. Some patients with IRDs may lose their vision gradually; others may be born with vision loss or lose their vision in infancy or early childhood. RPE65-related inherited retinal dystrophy (RPE65-IRD), which comprises RPE65-LCA/Early Onset Severe Retinal Dystrophy (EOSRD) and typical Retinitis Pigmentosa type 20 (RP20), is expected to affect 1,000 to 2,000 persons in the United States (Lloyd et al., 2019).

Biallelic RPE65-mediated IRD is the most severe form of IRD and arises when both alleles of the RPE65 gene in retinal pigment epithelium (RPE) cells are mutated. Mutations in the RPE65 gene diminish or eliminate the isomerohydrolase activity of RPE65. In the absence of RPE65, toxic precursors accumulate, RPE-producing cells are damaged, and photoreceptors are damaged over time, leading to almost complete blindness in most cases. Restoring the missing enzyme results in restoration of the visual cycle and improvement in vision RPE65-mediated IRDs can be confirmed by genetic testing, patient history, physical examination, and other diagnostic procedures (e.g., electroretinogram, dark adaptometry, kinetic perimetry, electrooculogram, optical coherence tomography, fluorescein angiography). 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.

Gene therapy augments, replaces, or suppresses missing or mutated, dysfunctional genes with functional gene copies using a vector to carry the functional gene into the cell. The goal is to address the root cause of an inherited disease and provide a lasting therapeutic effect by enabling the affected cells or organs to produce normally functioning protein(s) or discontinue production of harmful protein(s), potentially restoring normal function in diseased cells or organs and slowing or reversing disease progression. The retina is a particularly well-suited organ for gene therapy intervention due to its accessibility, immune privilege (e.g., tolerance to the introduction of antigens without eliciting an inflammatory immune response), small tissue size, and compartmentalization.

Luxturna (voretigene neparvovec-rzyl), referred to in this policy as voretigene, is a recombinant DNA-based adeno-associated virus (AAV) intended to deliver a normal copy of the gene encoding RPE65 to retinal cells in patients with low or missing amounts of biologically active RPE65. The protein that transforms light into an electrical signal in the retina is then produced by the retinal cells. Voretigene is a non-replicating, live AAV serotype 2 (AAV2) vectors developed to express the human RPE65 gene. Because AAV2 can efficiently infect RPE cells, where RPE65 is normally found, and generate sustained levels of gene expression, it is used to treat RPE65-dependent IRDs. AAV2 gene therapy introduces a normal copy of the gene into the cell as free-floating DNA outside of the chromosomes, rather than fixing or removing the defective gene.

Luxturna is the first FDA-approved gene therapy to treat visual loss caused by IRD caused by confirmed biallelic RPE65 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 open-label, randomized controlled trial (RCT) phase 3 efficacy and

safety study (n=31) in pediatric and adult participants with biallelic RPE65 mutation-associated retinal dystrophy and sufficient viable retinal cells (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.*

   Informational Note: Luxturna has only been studied for IRDs due to biallelic RPE65 mutations. There is no evidence for IRDs due to other mutations. Because diagnosis based on clinical symptoms of visual impairment can be difficult, and often different mutations can have a similar clinical presentation, the genetic testing for patients with IRD is recommended (AAO, 2016). 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.

AND

2. Presence of **viable retinal cells** as evidenced by optical coherence tomography (OCT) imaging and/or ophthalmoscopy documented by:
   a. An area of retina within the posterior pole of >100 µm thickness; **OR**
   b. Greater than or equal to 3-disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; **OR**
   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.

AND

3. Luxturna treatment requested for ONE of the following. Documentation required:
   a. Left eye; or
   b. Right eye; or
   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

AND

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.

AND

5. Member has NOT previously been: [ALL]
   a. Enrolled in clinical trials of gene therapy for retinal dystrophy RPE65 mutations; **AND**
   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; **AND**
   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.

AND

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 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 and 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.

AGE RESTRICTIONS: 3 years of age to less than 65 years of age at the time of therapy initiation

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 age 65 year and over. The safety and effectiveness of Luxturna have not been established in geriatric patients.

DOSING CONSIDERATIONS:

1. Usual recommended dose: 1.5×10^{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; **AND**
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 (1.5×10^{11} vg) per eye; **AND**
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.

DRUG INFORMATION

This section is intended solely for informative purposes. FDA approval is not a sufficient basis for coverage.

ROUTE OF ADMINISTRATION: Subretinal Injection

DRUG CLASS: Gene Therapy, Adeno-Associated Virus

FDA-APPROVED USES: Retinal dystrophy
Treatment of confirmed biallelic RPE65 mutation-associated retinal dystrophy

COMPENDIAL APPROVED OFF-LABELED USES: None

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. 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. 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. 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. 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 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.

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.

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

A Precision Therapy Assessment addressing *Voretigene Neparvovec-rzyl (Luxturna) for Inherited Retinal Dystrophies* concluded potential but unproven benefit for the treatment of vision loss due to IRD from confirmed biallelic RPE65 mutations in pediatric and adult patients. A very limited, low-quality body of evidence suggests that voretigene may be preferable to no treatment for visual function, with potential benefits lasting up to 4 years. Although preliminary limited data indicate that there are few significant AEs, evidence from a wider population is required to substantiate these findings. Lack of studies, patients, follow-up, and patient-reported results creates substantial uncertainty. Additional studies, albeit challenging due to the rarity of the condition, would support initial findings, fill in gaps in the evidence, and define patient selection criteria. (Hayes, 2021).

National and Specialty Organizations

The American Academy of Ophthalmology (AAO) (2012) issued eye care guidelines for patients with inherited retinal disease. These guidelines focus on the diagnosis and screening of IRDs. Genetic testing and screening were particularly emphasized; however, treatment options were not discussed since there were few or no treatments available for 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 caused by IRD from confirmed biallelic RPE65 mutations and who have 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 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	Description
67036	Vitrectomy, mechanical, pars plana approach
67299	Unlisted procedure, posterior segment

HCPCS	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 (5×10^{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 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

8/10/2022 Policy reviewed. No coverage criteria changes. Minor revisions, including clarification and addition of language, however no change to intent.

8/11/2021 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:

- 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');
- 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;
- Added criterion: Luxturna treatment requested for: Left eye, OR Right eye, OR Both eyes AND If request is for BOTH eyes: 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).

6/14/2018 Policy developed. IRO Peer Review: 2/5/2018. Practicing Physician. Board certified in Retinal Surgery.

REFERENCES

Government Agencies

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database (no National Coverage Determination identified). Available from CMS.
2. United States Food and Drug Administration (FDA). Cellular and gene therapy products: Luxturna (STN 125610). Updated June 9, 2022. Available from FDA. Accessed June 2022.
3. [1] United States Food and Drug Administration (FDA). Biologics License Application (BLA) approval letter. Available from FDA. Published December 19, 2017. Accessed June 2022.
4. [2] 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. Available from FDA. Published December 18, 2017. Accessed June 2022.
5. [3] United States Food and Drug Administration (FDA). BLA clinical review memorandum. Available from FDA. Published December 16, 2017. Accessed June 2022.
6. [4] United States Food and Drug Administration (FDA). FDA Advisory Committee briefing document: Spark Therapeutics, Inc. – Luxturna (voretigene neparvovec). Available from FDA. Published October 12, 2017. Accessed June 2022.

Prescribing Information and Drug Compendia

1. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. Available from ClinicalKey. Published 2022. Accessed April 2022. Registration and login required.
2. Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Available from Wolters Kluwer Health, Inc. Accessed April 2022. Registration and login required.
3. Luxturna (voretigene neparvovec-rzyl) [prescribing information]. Philadelphia: Spark Therapeutics Inc; September 2019. Available here.

Peer Reviewed Publications

1. 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. Accessed July 2022.
2. Hayes. Precision therapy assessment: Voretigene neparvovec-rzyl (Luxturna) for inherited retinal dystrophies. Published September 21, 2020. Updated October 28, 2021. Accessed June 2022. Registration and login required.
3. Lloyd A, Piglowska 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.
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. Accessed July 2022.

National and Specialty Organizations

1. American Academy of Ophthalmology. Recommendations on clinical assessment of patients with inherited retinal degenerations. Available from AAO. Published June 2016. Accessed July 2022.
2. Stone EM, Aldave AJ, Drack AV, et al. Recommendations for genetic testing of inherited eye diseases: Report of the American Academy of Ophthalmology Task Force on Genetic Testing. Ophthalmology. 2012;119(11):2408-2410. doi: 10.1016/j.ophtha.2012.05.047. Accessed July 2022.

3. National Institute for Health and Care Excellence (NICE). Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations (HST11). Available from NICE. Published October 9, 2019. Accessed June 2022.

Other Peer Reviewed Publications

1. 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). Available from ASGCT. Accessed July 2022.
2. 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. Accessed July 2022.
3. 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. Accessed July 2022.
4. [1] Garg S. Retinitis pigmentosa: Treatment. Available from UpToDate. Updated January 28, 2022. Accessed July 2022. Registration and login required.
5. [2] Garg S. Retinitis pigmentosa: Clinical presentation and diagnosis. Available from UpToDate. Updated February 1, 2022. Accessed July 2022. Registration and login required.Institute for Clinical and Economic Review (ICER). Voretigene neparvovec for biallelic RPE65-mediated retinal disease: Effectiveness and value – final evidence report. Available from ICER. Published February 14, 2018. Accessed July 2022.
6. 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. Accessed July 2022.
7. Maguire AM, High KA, Auricchio A, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: A phase 1 dose-escalation trial. Lancet. 2009 Nov 7;374(9701):1597-605. doi: 10.1016/S0140-6736(09)61836-5. Accessed July 2022.

APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*