Subject: Luxturna (Voretigene neparvovec-rzyl)	**Original Effective Date:** 7/10/2018
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. 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 (i.e., 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 document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Luxturna (Voretigene neparvovec-rzyl)**, a one-time gene therapy product indicated for the treatment of individuals with **confirmed bi-allelic RPE65 mutation-associated retinal dystrophy,** when appropriate criteria are met.

Voretigene neparvovec-rzyl is approved by the FDA as the originator biological product indicated for the treatment of patients with viable retinal cells and confirmed biallelic RPE65 mutation-associated retinal dystrophy.

The intent of the Luxturna (Voretigene neparvovec-rzyl) policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

- **Inherited retinal diseases** (also called inherited retinal dystrophies or IRD)
  - A group of rare blinding conditions caused by one of more than 220 different genes, including the RPE65 gene
  - A significant cause of blindness and decreased visual acuity in children and young adults
  - Some patients impacted by IRDs may experience a gradual loss of vision; others may be born with vision loss or experience vision loss in infancy or early childhood
  - The exact incidence of IRD associated with biallelic RPE65 mutations is unknown, though estimates indicate that approximately 1000 to 3000 patients in the United States may be affected (FDA 2017)

- **Treatment**
  - Prior to the approval of voretigene neparvovec, there were no pharmacological treatments for inherited retinal diseases. Standard of care included supportive services such as low-vision training and use of visual aid or adaptive mobility devices. Current care options include correction of refractive error and use of low-vision aids.
  - Gene Therapy (also known as gene augmentation therapy)
    - Genetic mutations in the human RPE65 protein lead to loss of visual function and retinal dystrophy.
    - Voretigene neparvovec is an adeno-associated virus vector-based therapy which has been genetically modified to contain a normal RPE65 gene. With use of the viral vector, the normal RPE65 gene is introduced into retinal epithelial cells and has the potential to increase normal RPE65 protein activity in retinal cells and restore the visual cycle.
    - Voretigene neparvovec allows for the introduction of a healthy RPE65 gene into the retina, but would not repair or eliminate the defective gene.
    - The eye is an ideal organ for gene-replacement therapy given its accessibility, immune privilege (i.e., tolerance to introduction of antigens without eliciting an inflammatory immune response), small size and compartmentalization
    - The goal is to enable, through the one-time administration of gene therapy, a lasting therapeutic effect
  - **Luxturna (Voretigene neparvovec)**
    - Indicated as a **one-time gene therapy** for the treatment of patients with vision loss due to confirmed biallelic RPE65-mediated inherited retinal dystrophies.
    - The **first gene replacement therapy** approved in the US that targets a disease caused by mutations in a specific gene
    - The first and only pharmacologic treatment for vision loss due to biallelic RPE65-mediated inherited retinal disease (IRD), also known as Leber congenital amaurosis type 2 (LCA2)
    - Administered to the retinal pigment epithelium by sub-retinal injection
    - **The use of Voretigene neparvovec (Luxturna) is supported by the FDA indication, and clinical trials which demonstrate improved light sensitivity, visual fields, and navigational ability under dim light situations**

- **CLINICAL EVIDENCE**
  - There are multiple published reports of very small phase I/II trials, however **the best evidence published at this time is a single phase 3 trial;** 20 participants in this trial received treatment
  - **FDA approval was primarily based on the results of a single, open-label, †crossover, fair quality,* phase 3 RCT (n=31) evaluating efficacy and safety in patients with retinal dystrophy associated with confirmed biallelic RPE65 mutations (Study 301)**

    **The trial was rated as 'fair quality' using criteria published by the US Preventive Services Task Force (USPSTF). (ICER 2018)*

    †Following the one-year control period of the Phase 3 study, all control participants elected to cross over and received Luxturna; long-term safety and efficacy continue to be assessed
  - The primary outcome measure in this trial is the MLMT, a novel functional vision test that has not been used as an efficacy endpoint in any other clinical studies.
    - Primary endpoint of mean bilateral MLMT change score (patients' ability to navigate a mobility course under a variety of specified light levels)
    - **Gain in functional vision** based on MLMT **in 93%** (27 of 29) with **72%** (21 of 29) achieving **maximum improvement** at the lowest light level evaluated (1 lux) at one year
    - Met two of three secondary endpoints
      - Full-field light sensitivity threshold (FST) testing averaged over both eyes (p=0.001) and the mobility test score change for the first injected eye (p=0.001)

- A third secondary endpoint, the change in visual acuity (VA) averaged over both eyes, was not statistically significant between intervention and control participants (p=0.17)

- **Voretigene neparvovec significantly improved functional vision compared with control at 1 year, and was maintained for 2 years in a randomized trial in adult and pediatric patients with biallelic RPE65 mutation-associated retinal dystrophy (Russell S, et al).**
- Safety analysis from the FDA included data from a phase 1 (n=12) and phase 3 trial (n=31). In the phase 1 study, bilateral injections were given to patients in both eyes at intervals of 1.7 to 4.6 years. In the phase 3 study, bilateral injections were only separated by 6 to 18 days. Overall, attrition was low; 2 patients in the phase 3 trial withdrew prior to treatment administration. (Luxturna Clinical Review. US FDA CDER)
- The most common adverse reactions (incidence greater than or equal to 5 %) in the clinical trials were cataract, conjunctival hyperemia, increased intra-ocular pressure, retinal tear, dellen, macular hole, sub-retinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy.
- **Immunogenicity** Immune reactions and extra-ocular exposure voretigene neparvovec in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. Study participants received systemic corticosteroids before and after subretinal injection of voretigene neparvovec to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

- **At this time, long-term data to establish the durability of responses to voretigene neparvovec is lacking.** Follow-up study is required to confirm long-term benefit and validate the findings of the phase 3 trial.
  - Clinical studies of voretigene neparvovec for the treatment of biallelic RPE65-mediated inherited retinal diseases have been favorable; however, long-term safety and efficacy data and duration of treatment effect is expected since fewer than 50 individuals have received treatment worldwide, and published follow-up data is less than three years in any participant.
  - **The manufacturer of voretigene neparvovec intends to follow all subjects out to 15 years per regulatory requirements.** (ICER 2018)
  - In clinical trials with data up to 1 to 2 years following administration, 2 patients had treatment-related serious ocular events (endophthalmitis and permanent vision loss) [Reference: Luxturna Clinical Review. US FDA, CDER]

- **CLINICAL GUIDELINES**
  - No guidelines published or identified addressing gene therapy as a treatment for IRDs at the time of this writing.
  - 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. These guidelines do not discuss treatment options as, until now, there have been few or no treatments available to individuals with IRDs.

CLASSIFICATION: Gene Therapy, Adeno-Associated Virus

FDA INDICATIONS

- **Retinal dystrophy** Treatment of confirmed biallelic *RPE65* mutation-associated retinal dystrophy
  - *Breakthrough therapy designation, rare pediatric disease designation, and orphan drug designation.*

Available as: A suspension supplied in a 0.5 mL extractable volume in a 2 mL single-dose vial; the supplied concentration (5 x 1012 vg/mL) requires a 1:10 dilution prior to administration.

FDA Approved: December 19, 2017

Black Box Warnings: None at the time of this writing

REMS: No REMS at the time of this writing

RECOMMENDATIONS/COVERAGE CRITERIA

Luxturna (Voretigene neparvovec-rzyl) adeno-associated virus vector-based gene therapy subretinal injection may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

❒ Prescribed by, or in consultation with, an ophthalmologist or retinal surgeon with experience providing sub-retinal injections. Submit consultation notes if applicable.

NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]
Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis

❒ Diagnosis of confirmed ***biallelic** RPE65 mutation-associated retinal dystrophy [*Biallelic mutation is a mutation on both copies of the RPE65 gene (affecting the function of both copies) and cause Leber Congenital Amaurosis, type 2 (LCA2), Early Onset Severe Retinal Dystrophy (EOSRD) and Severe Early Childhood-onset Retinal Dystrophy (SECORD), Retinitis Pigmentosa type 20 (RP20)]
Spark Therapeutics may offer access to genetic testing designed to identify biallelic RPE65 mutations. More information about the program and eligibility requirements available through manufacturer www.luxturna.com

Informational Note
- *Voretigene neparvovec (Luxturna) has only been studied for inherited retinal dystrophies (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 American Academy of Ophthalmology does recommend genetic testing for patients with inherited retinal diseases (AAO 2016).*

❒ Presence of **viable retinal cells** as evidenced by optical coherence tomography (OCT) imaging and/or ophthalmoscopy: [ONE]
- ❍ An area of retina within the posterior pole of >100 µm thickness
  OR
- ❍ 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° of fixation as measured by III4e isopter or equivalent

Informational Note: 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. Age/Gender/Restrictions [ALL]

- ❒ 3 years of age to less than 65 years of age at the time of therapy initiation
  - *Voretigene neparvovec-rzyl was studied in a randomized, controlled, open-label, phase 3 study. 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 (Voretigene neparvovec-rzyl) 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 voretigene have not been established in geriatric patients.*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ 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)
  - *Voretigene neparvovec has not been studied after or in combination with other gene therapies*

- ❒ Member has **not** received intraocular surgery within prior 6 months

5. Contraindications*Exclusions/Discontinuations

** Voretigene neparvovec-rzyl carries no black box warnings or contraindications*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to Luxturna (Voretigene neparvovec-rzyl) or any component of the formulation

Exclusions

- ❒ Previous treatment with Luxturna (Voretigene neparvovec-rzyl) or other gene therapy or in combination with other gene therapy in the requested/intended treatment eye(s)
- ❒ Pre-existing eye conditions or complicating systemic diseases that would eventually lead to irreversible vision loss and prevent full benefit of requested Luxturna (Voretigene neparvovec-rzyl) therapy
- ❒ Immunodeficiency (acquired or congenital) due to susceptibility to opportunistic infection (e.g., cytomegalovirus retinitis)
- ❒ Intraocular surgery within prior 6 months
- ❒ Pregnancy or Breastfeeding
  - *Adequate and well-controlled studies with voretigene have not been conducted in pregnant women.*
  - *There is no information regarding the presence of voretigene in human milk, the effects on the breastfed infant, or the effects on milk production.*

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Luxturna (Voretigene neparvovec-rzyl) is <u>not</u> authorized when used as re-treatment.

Re-treatment and repeated doses with Luxturna (Voretigene neparvovec-rzyl) has not been studied.

At the current time, the safety and efficacy of repeat injections into 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 (Voretigene neparvovec-rzyl)) are needed to determine the role of retreatment and to identify safety issues with repeat dosing.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

Retinal Dystrophy

- ❒ **≥12 months of age:** 1.5×10^{11} vector genomes (vg) administered via subretinal injection in a total volume of 0.3 mL. Administration to each eye should be performed on separate days (within a close interval), at least 6 days apart

- ❒ **Concomitant medication:** Systemic oral corticosteroids equivalent to prednisone 1 mg/kg/day (maximum: 40 mg/day) for a total of 7 days (starting 3 days before administration of voretigene neparvovec-rzyl to the first eye), and followed by tapering the dose during the following 10 days.

  The same corticosteroid dosing regimen applies for administration to the second eye. If the corticosteroid taper to the first eye is not complete 3 days prior to the planned administration to the second eye, then the corticosteroid regimen for the second eye replaces the taper for the first eye.

2. Authorization Limit [ALL]

- ❒ Quantity limit
  - ❍ **Maximum dose:** 1.5 x 10 vg administered one time by subretinal injection in a total volume of 0.3 mL per eye
  - ❍ ONE (1) injection per eye: **1.5 x 10 vg per eye**
  - ❍ **LIFETIME LIMIT:** Two treatment courses (one per eye)

- ❒ Approval duration: 4 weeks (1 lifetime dose per eye)
  - ◆ *Greater than 6 days but no more than 18 days have passed since treatment of the first eye. Due to significant safety concerns associated with immunogenicity against the vector and/or expressed protein, treatment of the second eye should be within 18 days of treatment of the first eye, but no fewer than 6 days apart.*

- ❒ Continuation of treatment: Luxturna (Voretigene neparvovec) is **not** authorized when used as re-treatment.
  - ◆ No clinical data are available on repeat administration of Luxturna to treat an individual eye. In clinical studies, patients received treatment in each eye once.

3. Route of Administration [ALL]

- ❒ Luxturna (Voretigene neparvovec) is considered a **provider-administered** medication via **subretinal injection** by a surgeon experienced in performing intraocular surgery.

- ❒ Use of voretigene neparvovec (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

COVERAGE EXCLUSIONS

This policy addresses the coverage of **Luxturna (Voretigene neparvovec-rzyl)** is a gene therapy used for the treatment of patients with vision loss due to **confirmed biallelic RPE65 mutation-associated retinal dystrophy** when appropriate criteria are met.

All other uses of **Luxturna (Voretigene neparvovec-rzyl)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY OF CLINICAL EVIDENCE

PIVOTAL TRIALS

The safety and efficacy of **Luxturna (Voretigene neparvovec)** was established with three open-label studies (two open-label Phase 1 trials and one open-label, randomized, controlled Phase 3 trial): one open-label, dose-exploration Phase 1 safety study (n=12) and one open-label, randomized, controlled Phase 3 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 Trials
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

- 12 patients with biallelic RPE65-mediated IRD (J Bennett et al)
- Subjects were predominantly white (92%) and male (58%) with an age range of 8 to 44 years.
- Treated with subretinal injections of Luxturna in one eye and were followed for 1 year prior to getting the injection into their second eye
- In a follow-on of this trial that included 11 of the original 12 patients, Luxturna was injected into the contralateral eye 1.7-4.6 years after administration in the first eye. All patients received the highest dose of Luxturna used in the previous trial (1.5×10^{11} vector genomes).
- All patients showed sustained improvements in retinal and visual function; children showed the greatest improvement (AM Maguire et al.)
- This cohort of participants (n=11) received the same dose of Luxturna that was administered in the Phase 3 trial and would have met the Phase 3 eligibility criteria
- Significant improvements from baseline in mobility testing and full-field light sensitivity, the main efficacy outcomes, occurred in the injected eye by day 30 and persisted to year 3, but there were no significant changes in visual acuity from baseline to year 3 (J Bennett et al)

Phase 3 Trial

The Phase 3 study was an open-label, randomized, controlled, and cross-over trial, designed to evaluate efficacy and safety of sequential subretinal injection of voretigene neparvovec to each eye.

Inclusion

- Age > 3 years (participants were 4 to 44)
  - 31 patients; 4 to 44 years old; mean age 15 years
  - Twenty-one subjects were randomized to treatment (n=21) and 10 were randomized to control with no treatment and the option for treatment after one year (delayed intervention arm) (n=10)
  - Confirmed biallelic RPE65 mutations
- Presence of sufficient viable retinal cells for therapy (area of retina within posterior pole > 100 microns thickness)
- Visual acuity worse than or equal to 20/60 for both eyes and/or a visual field less than 20 degrees in any median
- Treatment included a bilateral, subretinal injection of voretigene neparvovec (0.3 mL) with the second eye being treated 6-18 days after the first eye.
- Ability to perform standardized multi-luminance mobility testing (MLMT) within the luminance range evaluated and an MLMT* score worse than 1 lux and accuracy of less than or equal to 1 at 400 lux

  **The MLMT was created by the study sponsor in conjunction with the FDA to define a quantifiable measure of functional vision that incorporates aspects of visual acuity, visual field, and light sensitivity. The MLMT, an obstacle course, was the tool used to determine efficacy of the treatment. Throughout the study, subjects had to navigate the MLMT independently and accurately under differing light conditions with a 3-minute time limit and a maximum allowance of 3 errors. There are 12 different light levels from 1 lux (moonless summer night) to 400 lux (office environment or food court).*
- Primary endpoint: Change in bilateral MLMT performance from baseline to one year after treatment
  - A change of one light level in passing was considered clinically meaningful (by the study sponsor)
  - One year after treatment, 13 of the 20 subjects (65%) in the active group were able to complete the MLMT at the lowest light level of 1 lux; none of the subjects in the control group were able to do this
  - Overall, 21 of 29 subjects achieved the maximum possible MLMT improvement over 1 year and over 2 years in the original intervention group.
- Results
  - The results show that participants treated with Luxturna saw a difference of 1.6 (95% CI, 0.72 to 2.41) in their bilateral MLMT change score at one year compared to placebo (intervention arm score improvement of 1.8, control arm score improvement of 0.2). (Russell S, et al) This result indicates that participants treated with Luxturna were able to see in lower light conditions.
  - The efficacy of Luxturna was established on the basis of multi-luminance mobility testing (MLMT) score change from baseline after one year, which measured changes in functional vision. At one year, mean bilateral **MLMT change score was 1.8 light levels for patients receiving Luxturna versus 0.2 in the control group** (difference of 1.6, 95% CI 0·72–2·41, p=0·0013). 65% of patients receiving Luxturna passed MLMT at the lowest luminance level tested, demonstrating maximum possible improvement.
  - **Improvement had occurred by day 30 following treatment and was maintained throughout a 2-year follow-up period.**
  - **Data show mean improvement demonstrated at one year post one-time administration maintained through at least three years for original intervention cohort, and two years for crossover cohort, with observation ongoing**
    - The mean MLMT improvement measured 1.8 lux levels at three years, compared to 1.9 lux levels at one year.

- The more than 100-fold average improvement in FST testing observed in the intervention group at one year similarly was maintained through at least three years.
- Additionally, the increase in visual acuity (VA) averaged over both eyes, a secondary endpoint which was not statistically significant at one year, has been stable for at least three years for participants in the intervention cohort, at an eight-letter improvement using standardized VA testing.

- **At one year,** the median MLMT score had increased by 2 light levels in the treatment group versus 0 in the control group, a statistically significant difference.
- **Two-year data** [presented at the Association for Research in Vision and Ophthalmology (ARVO)] meeting in May 2017 (ARVO; Russell S). Treated patients also showed improvement in tests of full-field light sensitivity threshold, visual fields, and best-corrected visual acuity, compared to controls (J Bennett et al) (FDA Clinical Review. Voretigene neparvovec-rzyl. December 16, 2017)
- **Three-year data** (presented at the ARVO meeting in November 2017) showed sustained benefits at three years for the intervention group and at two years for the delayed intervention arm.
  - Three years after the one-time administration of Luxturna to both eyes, the cohort of 20 participants in the modified intent-to-treat (mITT) intervention group maintained the average improvement demonstrated at one year, as measured by MLMT score change, the primary endpoint, and full-field light sensitivity threshold (FST) testing, a secondary endpoint.

- Three secondary endpoints were evaluated in a hierarchical order: full-field light sensitivity (FST) using white light averaged over both eyes, monocular MLMT score change for the first treated eye, and visual acuity averaged over both eyes
  - The BCVA scores in the intervention group did show an insignificant numerical improvement over the control group. The authors noted this was not unexpected as BCVA is a measure of foveal, cone-mediated function, and the RPE65 gene mutations result in a rod-mediated disease
- Adverse events were mostly ocular were mild in severity
  - No product-related serious adverse events or deleterious immune responses occurred
  - The most common adverse events noted 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) (PI)

- **Authors of the phase 3 clinical trial concluded that treatment with Luxturna improved light sensitivity, visual fields, and navigational ability under dim light in patients who have no treatment alternatives. (Russell S, et al.)**

Serious Adverse Events (SAEs)

Two ocular SAEs were reported in the clinical program.

- There was one SAE related to the surgical procedure in one eye of a Phase 3 participant, in which there was foveal thinning and a sustained reduction in VA. One additional ocular SAE was reported in one eye of a Phase 1 participant in which the treatment for bacterial endophthalmitis led to elevated intraocular pressure and subsequent optic atrophy.
- There were three non-serious AEs of retinal deposits (subretinal precipitate) in three participants (three eyes) that were considered to be related to Luxturna. All three of these events were mild in intensity, transient in nature and resolved without consequences.
- No harmful immune responses have been observed.
- The most common adverse reactions related to Luxturna reported in 10 percent or greater of the combined Phase 1 and Phase 3 trial participants included conjunctival hyperemia, cataract, increased intraocular pressure and retinal tear.

CLINICAL PRACTICE GUIDELINES

No guidelines published or identified addressing gene therapy as a treatment for IRDs at the time of this writing.

- 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. These guidelines do not discuss treatment options as, until now, there have been few or no treatments available to individuals with IRDs.

DEFINITIONS

- **Adeno-associated viruses (AAV)**
  AAVs 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.

- **Gene Therapy**
  The American Society of Gene & Cell Therapy defines gene therapy as a set of strategies that modify the expression of an individual's genes or repair abnormal genes. Each strategy involves the administration of a specific nucleic acid (DNA or RNA). Nucleic acids are normally not taken up by cells, thus special carriers, so-called 'vectors' are required. Vectors can be of either viral or non-viral nature (American Society of Gene & Cell Therapy)

- **Multi-luminance Mobility Testing (MLMT)**
  The 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 MLMT was completed with one eye patched, another MLMT was completed with the other eye patched, and a third MLMT was completed with both eyes open. These attempts were videotaped and scored on a pass/fail basis by 2 masked independent graders. There were 12 different courses with the same number of turns and obstacles. 12 different light levels from 1 lux (moonless summer night) to 400 lux (office environment or food court).

  MLMT score change was defined as the difference between the score at baseline and the score at one year with a positive score change indicating that a participant was able to complete MLMT at a lower light level.

  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 Gene**
  Retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA) both have subtypes related to pathogenic variants in *RPE65*. *RPE65* (retinal pigment epithelium–specific protein 65-kD) gene encodes the RPE54 protein is an all-*trans* retinal isomerase, a key enzyme expressed in the retinal pigment epithelium (RPE) that is responsible for regeneration of 11-*cis*-retinol in the visual cycle. The *RPE65* gene is located on the short (p) arm of chromosome 1 at position 31(1p31.3). 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.

APPENDIX

N/A

CODING INFORMATION

The codes listed in the policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

CPT	Description
67028	Intravitreal injection of a pharmacologic agent (separate procedure)
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-hyphen25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-hyphen50 exons, cytogenomic array analysis for neoplasia)
92134	Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; retina
92225	Ophthalmoscopy, extended, with retinal drawing (e.g., for retinal detachment, melanoma), with interpretation and report, initial

HCPCS	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10	Description [For dates of service *on or after* 10/01/2015]
H35.50	Unspecified hereditary retinal dystrophy [bi-hyphenallelic RPE65 mutation-hyphenassociated retinal dystrophy]
H35.52	Pigmentary retinal dystrophy
H35.54	Dystrophies primarily involving the retinal pigment epithelium

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REFERENCES

PACKAGE INSERT, FDA, DRUG COMPENDIA

Luxturna [prescribing information]. Philadelphia, PA; Spark Therapeutics, Inc. December 2017.

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at www.clinicalpharmacology.com. Accessed May 2018. [Available with subscription]

.

Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Clinical Drug Information LLC, 2018. Available from Wolters Kluwer Health, Inc. Accessed May 2018. [Available with subscription]

Micromedex Healthcare Series [database online]. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc. Updated periodically. http://www.thomsonhc.com. Accessed May 2018. [Available with subscription].

Food and Drug Administration. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. FDA: Silver Spring, MD. December 19, 2017. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm. Accessed April 2018.

Luxturna Clinical Review. US Food and Drug Administration Center for Drug Evaluation and Research. Available at: https://www.fda.gov/downloads/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/ucm592766.pdf Accessed April 2018

U.S. Food and Drug Administration. Advisory committee briefing document on Voretigene Neparvovec (BLA 125610). [cited 11/06/2017]; Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM579290.pdf. Accessed April 2018

FDA Advisory Committee Briefing Document: Spark Therapeutics, Inc., Luxturna (voretigene neparvovec). 2017; Available at: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/cellulartissueandgenetherapiesadvisorycommittee/ucm579300.pdf. Accessed April 2018

Spark Therapeutics [Internet]. Philadelphia: Spark Therapeutics, Inc. Spark Therapeutics' Biologics License Application for investigational voretigene neparvovec accepted for filing by FDA; 2017 Jul 17 [cited 2018 April]. Available at: http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-biologics-license-application-investigational Accessed April 2018.

Spark Therapeutics. Voretigene briefing information. Website. October 12, 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM579300.pdf. Accessed April 2018.

CLINICAL TRIALS, DEFINITIONS, PEER-REVIEWED PUBLICATIONS

Campa C, Gallenga CE, Bolletta E, et al. The role of gene therapy in the treatment of retinal diseases: a review. ***Curr Gene Ther.*** Nov 16 2017;17(3):194-213. PMID 29149824

Maguire AM et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. Lancet 2009; 374:1597.

J Bennett et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial. Lancet 2016; 388:661.
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 randomized, controlled, open-label, phase 3 trial. Lancet. 2017; 390(10097):849-860. PMID 28712537

ARVO. Russell S, Bennett J, Wellman J, et al. Two-Year Results for a Phase 3 Trial of Voretigene Neparvovec in Biallelic RPE65-mediated Inherited Retinal Disease. Paper presented at: ARVO2017; Baltimore, MD.

ARVO. Russell S, Bennett J, Wellman J, et al. Phase 3 Trial Update of Voretigene Neparvovec in Biallelic *RPE65* Mutation-Associated Inherited Retinal Disease. Paper presented at: Annual Meeting of Ophthalmology2017; New Orleans, LA.

GOVERNMENT AGENCIES, PROFESSIONAL SOCIETIES, OTHER AUTHORITATIVE PUBLICATIONS

American Academy of Ophthalmology. Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations 2016. Available at: https://www.aao.org/clinical-statement/recommendations-on-clinical-assessment-of-patients#GeneticTestingandGeneticCounseling. Accessed May 2018

American Society of Gene & Cell Therapy. Gene therapy vs. cell therapy. Available at: http://www.asgct.org/about_gene_therapy/genevscell.php. Accessed May 2018

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.

Institute for Clinical and Economic Review. Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. Final Evidence Report. February 14, 2018. Available at: https://icer-review.org/material/voretigene-evidence-report/. Accessed May 2018

Policy History	MCPC
Policy Developed *Peer Review: AMR Peer Review Network. 2/5/2018. Practicing Physician. Board certified in Retinal Surgery*	6/14/18

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