Medical Policy Bulletin
Title:
Voretigene Neparvovec-rzyl (Luxturna®)
Policy #:
08.01.44c

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's contract.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

Voretigene neparvovec-rzyl (Luxturna™) is considered medically necessary and, therefore, covered for the treatment of individuals with confirmed biallelic *RPE65* variation(s) causing retinal dystrophy who are experiencing vision loss when all of the following criteria are met:

- Documentation of laboratory results confirming biallelic *RPE65*variation(s) causing retinal dystrophy
- Individual has viable retinal cells, as determined by the treating retinal specialist, and characterized by at least one of the following features:
    - An area of retina within the posterior pole of >100 µm thickness shown on optical coherence tomography
    - ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole
    - remaining visual field within 30° of fixation as measured by III4e isopter or equivalent
- Age of individual is 3 years to less than 65 years of age
- Administration will occur at a certified treatment center staffed with professional providers, including retinal specialists, who have experience treating individuals with inherited retinal diseases
- Verification that a baseline full-field light sensitivity threshold (FST) test has been performed
- Individual does not have any of the following exclusion criteria:
    - Use of high-dose (>7500 retinol equivalent units [or >3300 IU] per day of vitamin A) retinoid compounds in the past 18 months
    - Intraocular surgery in the past 6 months
    - Ocular or systemic conditions that would interfere with this gene therapy
    - Pregnant individuals or individuals of child-bearing potential who are unwilling to use effective contraception for 4 months after vector administration

EXPERIMENTAL/INVESTIGATIONAL

All other uses for voretigene neparvovec-rzyl (Luxturna™), including the retreatment of the same eye(s) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

Full-field light sensitivity threshold (FST) testing is a measure of visual function that tests the underlying physiologic function of the rod photoreceptors. FST testing prior to therapy is an important measurement to establish an individual's baseline functioning; additionally, FST testing at 30 days post-therapy determines effectiveness. If voretigene neparvovec-rzyl (Luxturna™) is effective, an individual's FST test results should show significant improvements over baseline testing. Due to the lack of long-term studies, FST testing is also recommended 30 months post-therapy to establish that voretigene neparvovec-rzyl (Luxturna™) has shown effectiveness over time.

The Treatment Center certified to administer voretigene neparvovec-rzyl (Luxturna™) must obtain the drug through the Spark PATH program. The Spark Path Program will direct ship the drug to the Treatment Facility through The Company-appointed Specialty Pharmacy whereby the Treatment Facility does not have to purchase or bill the drug. The Company-appointed Specialty Pharmacy will be responsible for billing the Company for the drug. The Treatment Facility will not receive reimbursement for the actual drug.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, voretigene neparvovec-rzyl (Luxturna™) is covered under the medical benefits of the Company's products when the medical necessity criteria listed in this medical policy are met.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Voretigene neparvovec-rzyl (Luxturna™) was approved by the FDA on December 19, 2017 for the treatment of individuals with confirmed biallelic *RPE65* mutation-associated retinal dystrophy after confirmation by the treating physician(s) that the individual has viable retinal cells.

Per the FDA-approved prescribing information:

> "Perform subretinal administration of voretigene neparvovec-rzyl (Luxturna™) to each eye on separate days within a close interval, but no fewer than 6 days apart.
>
> Treatment with voretigene neparvovec-rzyl (Luxturna™) is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and voretigene neparvovec-rzyl (Luxturna™) would potentially be diluted or lost during cell proliferation.
>
> The safety and efficacy of voretigene neparvovec-rzyl (Luxturna™) have been established in pediatric patients. Use of voretigene neparvovec-rzyl (Luxturna™) is supported by Study 1 and Study 2 that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups."

Description

Inherited retinal dystrophies (IRD) are a group of rare genetic diseases that result in blindness. The most common category of these diseases is retinitis pigmentosa (RP), a disorder that causes retinal cells to die, primarily affecting photoreceptor (rods and cones) and pigment epithelial function. RP leads to progressive retinal

degeneration and dysfunction and the loss of ability to transmit these visual electrical signals to the brain. Individuals with RP will experience vision symptoms, including night blindness, loss of central and peripheral vision (or "tunnel vision"), and nystagmus. Treatment to slow the progression includes light avoidance, use of low-vision aids, and vitamin A supplementation. Leber congenital amaurosis (LCA) is a less common but more severe form of RP that is present at birth. The visual impact includes early and rapid vision loss. Treatment of LCA includes correction of farsightedness and the use of low-vision aids. When left untreated, patients lose the ability to detect light of any intensity. They become severely limited in their ability to independently navigate, and any vision-dependent activities of daily living are impaired.

Individuals with IRD may have a genetic biallelic variation(s) in human retinal pigment epithelial-specific 65kDA protein (RPE65), that is critical for the regeneration of the visual pigment necessary for both rod and cone-mediated vision.

Voretigene neparvovec-rzyl (Luxturna™) was approved by the United States Food and Drug Administration (FDA) on December 19, 2017 for the treatment of individuals with confirmed biallelic *RPE65* mutation-associated retinal dystrophy after confirmation by the treating physician(s) that the individual has viable retinal cells.

Voretigene neparvovec-rzyl (Luxturna™) is an adeno-associated virus vector type 2 (AAV2) that contains a functioning copy of human RPE65 protein. It is intended as a one-time gene therapy to slow the disease progression to complete blindness by supplying the RPE65 protein into the targeted cells which will utilize the cell to express the protein, thereby regenerating the cells.

PEER-REVIEWED LITERATURE
Summary

The safety and effectiveness of voretigene neparvovec-rzyl (Luxturna™) in individuals ages 4 years or older with inherited retinal dystrophy were studied in a Phase 3, open-label, randomized, controlled trial over 1 year. Individuals were required to have a confirmed genetic diagnosis of biallelic *RPE65*gene variation(s), both eyes had visual acuity of 20/60 or worse or visual field less than 20 degrees in any meridian, or both. Other inclusion criteria were composed of: sufficient viable retinal cells as determined by retinal thickness on spectral domain optical coherence tomography (>100 microns within the posterior pole), fundus photography, and clinical examination; and the ability to perform a standardized multi-luminance mobility test (MLMT) (i.e., obstacle course) within the luminance range evaluated, but unable to pass the MLMT at 1 lux, the lowest luminance level tested (described as a moonless summer night or indoor nightlight).

Individuals were randomized (2:1) to receive voretigene neparvovec-rzyl (Luxturna™) (N=20) in the intervention group, or no injection in the control group (N=9). (The control group became eligible to receive voretigene neparvovec-rzyl (Luxturna™) 1 year after their baseline evaluations, provided they still met all of the eligibility criteria). The subretinal injection of 1.5×10^{11} vector genomes (vg) voretigene neparvovec-rzyl (Luxturna™) was administered under general anaesthesia. The first eye that was injected was chosen based on which eye had the worst visual acuity, subject preference, or both. The second eye was injected 6-18 days after the first procedure.

The primary efficacy endpoint was change in MLMT performance one year after baseline. Participants were assessed with MLMT at baseline, with subsequent assessments at 30, 90, 180, and 365 days after randomization (control group) or after the second injection (intervention group). MLMT was a 5' x 10' obstacle course created to evaluate vision by having participants navigate around obstacles in or adjacent to the path in varying environmental illuminations, including very low light levels, integrating aspects of visual acuity, visual field, and light sensitivity. Participants navigated the path with one eye patched, then another configuration of the path with the other eye patched, then again with both eyes open. This process was repeated with varying light levels to discover which levels caused participants to pass or fail the course. Passing was defined as completion of the course at the specified light level with fewer than four errors (corresponding to an accuracy score of <0.25) and within 3 minutes. Each light level was assigned a discrete lux score from 0 to 6, with lower light levels corresponding to higher lux scores. The graders who assessed primary outcome were masked to treatment group to avoid bias.

At the one-year mark, there was a statistically significant difference between treatment groups in regards to the mean bilateral MLMT change score (1.8 light levels in the intervention group versus 0.2 in the control group) (p=0.0013). Thirteen (65%) of 20 participants in the intervention group, but no participants in the control group, passed MLMT at the lowest luminance level tested (1 lux), demonstrating maximum possible improvement. All but one participant in the intervention group had advanced at least one light level.

One of the three secondary endpoints reviewed in the study was full-field light sensitivity threshold (FST) testing. FST

is a measure of visual function, generally assessed per eye, that tests the underlying physiologic function of the rod photoreceptors. FST measures the lowest illumination perceived (i.e., light sensitivity) over the entire visual field. FST test-retest variability has been stated as 0.3 log and a meaningful change has been suggested as 10 dB or 1 log. The results reported a statistically significant (p=0.0004) difference between the intervention and control group regarding the mean FST over 1 year of study.

There were no serious adverse events or deleterious immune responses caused by voretigene neparvovec-rzyl (Luxturna™). Most ocular events were mild in severity. Safety and efficacy will be monitored for at least 5 years through assessments at annual visits, including safety, mobility testing, and retinal and visual function testing, and for 15 years via questionnaires at annual visits or telephone visits.

Future studies will need to evaluate the outcomes in a larger sample size, determine which patient characteristics are most appropriate for treatment (e.g., age, visual acuity, how early in disease progression treatment is initiated), the longevity of treatment, the possibility for re-treatment, and the clinical relevance of various outcome measures.

OFF-LABEL INDICATION

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
H35.50 Unspecified hereditary retinal dystrophy
H35.51 Vitreoretinal dystrophy
H35.52 Pigmentary retinal dystrophy
H35.53 Other dystrophies primarily involving the sensory retina
H35.54 Dystrophies primarily involving the retinal pigment epithelium
Q14.1 Congenital malformation of retina

HCPCS Level II Code Number(s)
J3398 Injection, voretigene neparvovec-rzyl, 1 billion vector genomes

Revenue Code Number(s)
N/A

Coding And Billing Requirements

BILLING REQUIREMENTS

If there is no specific HCPCS code available for the drug administered, then the drug must be reported with the most appropriate unlisted code along with the corresponding National Drug Code (NDC).

Policy History

Revisions from 08.01.94c:

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
09/05/2023	This policy has been reissued in accordance with the Company's annual review process.
11/03/2021	This policy has been reissued in accordance with the Company's annual review process.

12/16/2020	This policy has been reissued in accordance with the Company's annual review process.
09/25/2019	This policy has been reissued in accordance with the Company's annual review process.
01/01/2019	This version of the policy will become effective 01/01/2019. This policy has been identified for the HCPCS code update, effective 01/01/2019. The following HCPCS code has been **added** to this policy: J3398 Injection, voretigene neparvovec-rzyl, 1 billion vector genomes The following HCPCS codes have been **removed** from this policy: C9032 Injection, voretigene neparvovec-rzyl, 1 billion vector genome J3490 Unclassified drugs J3590 Unclassified biologics

Revisions From 08.01.94b:

09/24/2018	This policy was updated to clarify language regarding: • Genetic testing of biallelic *RPE65* variation(s) causing retinal dystrophy • Full-field light sensitivity threshold (FST) testing • How to obtain voretigene neparvovec-rzyl (Luxturna™)

Revisions From 08.01.94a:

07/01/2018	This policy has been identified for the HCPCS code update, effective 07/01/2018. The following HCPCS code has been **added** and the corresponding non-specific code **removed** from this policy: **ADDED:** C9032 Injection, voretigene neparvovec-rzyl, 1 billion vector genome **REMOVED:** C9399 Unclassified drugs or biologicals

Revisions From 08.01.94:

02/07/2018	This new policy has been issued to communicate the Company's coverage position for voretigene neparvovec-rzyl (Luxturna™).

Version Effective Date:
01/01/2019
Version Issued Date:
01/02/2019
Version Reissued Date:
03/28/2025