Clinical Policy: Voretigene Neparvovec-rzyl (Luxturna)

Reference Number: OC.UM.CP.0087 Coding Implications
Last Review Date: 12/2021 Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Voretigene neparvovec-rzyl (Luxturna™) is an adeno-associated virus vector-based gene therapy.

FDA Approved Indication(s)

Luxturna is indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).

Policy/Criteria

Provider must submit documentation (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

All requests reviewed under this policy **require medical director review.**

It is the policy of health plans affiliated with Envolve Vision, Inc.® (Envolve) that Luxturna is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Retinal Dystrophy (must meet all)**:**

1. Diagnosis of retinal dystrophy confirmed by genetic diagnosis of biallelic *RPE65* gene mutations;
2. Prescribed by or in consultation with an ophthalmologist;
3. Age ≥ 3 years;
4. Member has not previously been treated with Luxturna in the requested treatment eye(s);
5. Sufficient viable retinal cells as evidenced by both of the following (a and b):
   a. Retinal thickness on spectral domain optical coherence tomography (i.e., areas of retina with thickness measurements > 100 microns within the posterior pole);
   b. Fundus photography (i.e., presence of neural retina);
6. Significant vision loss as evidenced by at least one of the following (a or b):
   a. Visual acuity of 20/60 or worse in both eyes (*see Appendix D*);
   b. Visual field less than 20 degrees in any meridian (*see Appendix D*);
7. Member has not received intraocular surgery within prior 6 months;
8. Full-field stimulus testing (FST) for blue and red light baseline score of > -2.00 log10(cd/m^2) (e.g., + 1.00 log10(cd/m^2);
9. Dose does not exceed 1.5 x 10^{11} vector genomes (vg) per eye.

Approval duration: 4 weeks (1 lifetime dose per eye)

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Retinal Dystrophy (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Greater than 6 days but no more than 18 days have passed since treatment of the first eye;
3. Request is not for a repeat treatment of a previously treated eye (*see Appendix D*);
4. Dose does not exceed 1.5×10^{11} vg per eye.

Approval duration: 4 weeks (1 lifetime dose per eye)

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
MLMT: multi-luminance mobility testing
RP: retinitis pigmentosa
vg: vector genomes

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- No clinical data are available on repeat administration of Luxturna to treat an individual 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.

- Due to the safety concerns related to subretinal injection procedure, as well as lack of evidence of clinical benefit in patients with greater baseline visual function than specified in the criteria, only patients with significant vision loss in both eyes are candidates for treatment at this time.
- 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. Viable retinal cells can be determined by the following:
  - Fundus photography documents the retina, the neurosensory tissue in our eyes through a specialized low power microscope with an attached camera.
  - Optical coherence tomography is a noninvasive imaging test that uses light waves to take cross-section pictures of the retina to visualize the retina's distinctive layers.
- Retinitis pigmentosa (RP) refers to a group of hereditary retinopathies or retinal dystrophies that affects about 2.5 million people worldwide. Mutations in human *RPE65* cause Leber congenital amaurosis and other forms of autosomal recessive RP, which are characterized by early-onset blindness. Leber congenital amaurosis occurs in 2 to 3 per 100,000 newborns and it is one of the most common causes of blindness in children.
- Multi-Luminance Mobility Testing (MLMT) description:
  - The MLMT is a task that challenges a subject to navigate a course independently and accurately under differing light conditions within a time limit. The test is conducted at seven different light levels, from 1 lux to 400 lux, which span a wide range of environmental lighting conditions commonly encountered during the course of everyday activities.
  - The inclusion criteria in the clinical trial of Luxturna (Study 301) required that the eligible patient be able to perform a standardized MLMT test within the luminance range evaluated, but unable to pass the MLMT at 1 lux, the lowest luminance level tested.

Light Level	MLMT Lux Score
1 lux	6
4 lux	5
10 lux	4
50 lux	3
125 lux	2
250 lux	1
400 lux	0

- Significant vision loss as evidenced by visual acuity (VA) description:
  - Visual acuity of 20/60 or worse in both eyes:
    - Visual acuity can be measured by a Snellen eye test chart or a LogMAR chart.
    - The Snellen chart has optotypes arranged 5 by 5 on a grid to indicate the letter size. VA is determined by the line that the person can recognize, and if that line is twice as large as the reference standard (20/20), that person's Magnification Requirement (MAR) is 2x. If the MAR is 2x, the VA is 1/2 (20/40), and would need 2x the magnification. Similarly if the MAR is 3x, the VA is 1/3 (20/60), and would need 3x magnification.
    - The LogMAR chart comprises of rows of letters and is used to estimate a more accurate visual acuity than other more commonly used charts (e.g., the Snellen

chart). Each letter in the LogMAR chart has a score value of 0.02 log units. Since there are 5 letters per line, the total score for a line on the LogMAR chart represents a change in 0.1 log units. The formula used in calculating the score is: [LogMAR VA = 0.1 + LogMAR value of the best line read – 0.02 X (number of letters read)]. Zero LogMAR indicates standard vision, while zero VA indicates blindness.

- The World Health Organization established criteria for low vision using the LogMAR scale, which is defined as a best-corrected visual acuity worse than 0.5 LogMAR but equal or better than 1.3 LogMAR in the better eye. Blindness is defined as a best-corrected visual acuity worse than 1.3 LogMAR.

- Visual field less than 20 degrees in any meridian:
  - Visual field is another distinct measurable function of the eye. It represents the visual area that is perceived simultaneously by a fixating eye.
  - The field of vision is that portion of space in which objects are visible at the same moment during steady fixation of gaze in one direction. The normal limits of the visual field consists of central vision, which includes the inner 30 degrees of vision and central fixation, and the peripheral visual field, which extends 100 degrees laterally, 60 degrees medially, 60 degrees upward, and 75 degrees downward.
  - Visual field can be measured by a **Goldmann Perimetry Test.**
    - Perimetry measures all areas of eyesight, including side, or peripheral, vision. Goldmann perimetry testing is the most widely used instrument for manual perimetry (meridian). It uses a specific background luminance and a bowl with a specific radius with a dotted stimuli that is used to plot an isopter, which is denoted by:
      - Roman numerals = 0 to V (size)
      - Number = 1 to 5 (Luminance) use of filter
      - Alphabet = a to e use of filter
    - Isopter: The line connecting all points in the visual field with the same threshold for a given test spot; boundary between area of visibility of the area of non-visibility for a particular stimulus.
    - Expected findings for normal isopters for those under 50 years of age are:
      - Peripheral: I-4e
      - Intermediate: I-3e
      - Central: I-2e
    - The visual field is considered abnormal if the threshold values are significantly brighter than the expected values.
    - Patients with a visual field less than 20 degrees in any meridian as measured by a **III4e isopter or equivalent** in both eyes show significant vision loss for treatment with Luxturna.

- Full-field Light Sensitivity Testing (FST) threshold:
  - FST is a method to quantify extremely abnormal visual perception, and it tests the patient's light sensitivity of the entire retina by measuring the patient's perception of different luminance levels. A light flashes inside of a dome accompanied by a beeping sound, and each time a beep sounds, the patient must indicate whether or not they saw a light by pressing a yes or no button. And this is repeated at different

intensities and an algorithm identifies the minimum luminance at which the patient reliably perceives light.
- The lower or more negative the FST score, the better the eye light sensitivity, and vice versa.
- In the Luxturna pivotal trial, all of the patients enrolled and treated had a baseline FST score of -2.00 or higher. According to Klen M. and the Retina Foundation of the Southwest, the median FST threshold of eyes of normal subjects tested were around -4.8 or lower, while a median threshold value of 0.9 +/- 1.4 log10 (cd/m^2) has been reported for patients with severe retinal degenerative disease with light perception.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Biallelic *RPE65* mutation-associated retinal dystrophy	1.5×10^{11} vg administered one time by subretinal injection in a total volume of 0.3 mL per eye	1.5×10^{11} vg/eye

VI. Product Availability

Single-dose vial: 5×10^{12} AAV2-hRPE65v2 vg/mL

VII. References

1. Luxturna Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; December 2017. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna. Accessed October 8, 2020
2. 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; 390:849-60. http://dx.doi.org/10.1016/
3. Dias MF, Joo K, Kemp JA, Fialho SL, da Silva Cunha A Jr, et al. Molecular genetics and emerging therapies for retinitis pigmentosa: Basic research and clinical perspectives. Prog Retin Eye Res 2017; pii: S1350-9462:30052-6. doi: 10.1016/j.preteyeres.2017.10.004. [Epub ahead of print]
4. U.S. National Library of Medicine. Leber congenital amaurosis. Genetics Home Reference. http://www.ghr.nlm.nih.gov/condition/leber-congenital-amaurosis#statistics. Accessed December 21, 2017.
5. Evans JM. Standards for visual acuity. Intelligent Systems Division: National Institute for Standards and Technology. June 2006. https://www.nist.gov/sites/default/files/documents/el/isd/ks/Visual_Acuity_Standards_1.pdf. Accessed December 21. 2017.
6. Klen M, the Retina Foundation of the Southwest. Psychophysical assessment of low visual function in patients with retinal degenerative disease (RDDs) with the Diagnosys full-field stimulus threshold (D-FST). Doc Ophthalmol. 2009; 119(3):217-224. doi:10.1007/s10633-009-9204-7.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3398	Injection, voretigene neparvovec-rzyl, 1 billion vector genomes

Reviews, Revisions, and Approvals	Date	Approval Date
Policy created	01/2018	02/2018
Policy adopted form Envolve Pharmacy following review by the Precision Drug Action Committee.	09/2020	10/2020
Annual Review; Added HCPCS code for Luxturna	12/2020	12/2020
Annual Review; Policy changes adopted form Envolve Pharmacy following review by the Precision Drug Action Committee: Converted HIM-Medical Benefit to HIM line of business references to HIM.PHAR.21 revised to HIM.PA.154; Added disclaimer under Policy/Criteria "All requests reviewed under this policy require medical director review."	12/2021	12/2021

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Envolve Vision, Inc., or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan

retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.