Clinical Policy Title:	voretigene neparvovec-rzyl
Policy Number:	RxA.402
Drug(s) Applied:	Luxturna®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
voretigene neparvovec-rzyl (Luxturna®)	Biallelic RPE65 mutation- associated retinal dystrophy	1.5×10^{11} vector genomes administered one time by subretinal injection in a total volume of 0.3 mL per eye	1.5×10^{11} vector genomes/eye

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Retinal Dystrophy (must meet all):

1. Diagnosis of retinal dystrophy, or Leber's congenital amaurosis (LCA), confirmed by genetic diagnosis of biallelic RPE65 gene mutations;
2. Prescribed and administered by an ophthalmologist or retinal surgeon with experience providing sub-retinal injections;
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 C*);*
   b. Visual field less than 20 degrees in any meridian (see Appendix C);
7. Member has not received intraocular surgery within prior 6 months;
8. Member meets one of the following (a or b):
   a. A baseline Multi-Luminance Mobility Testing (MLMT) score lower than 6 points (i.e., unable to pass at the lowest luminance level of 1 lux, see Appendix C);
   b. 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
Commercial: 28 days (1 lifetime dose per eye)
Medicaid: 28 days (1 lifetime dose per eye)

II. Continued Therapy Approval

A. Retinal Dystrophy (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
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 C);
4. Dose does not exceed 1.5 x 10^{11} vg per eye.

Approval Duration
Commercial: 28 days (1 lifetime dose per eye)
Medicaid: 28 days (1 lifetime dose per eye)

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
MLMT: Multi-Luminance Mobility Testing
RP: Retinitis Pigmentosa
LCA: Leber's Congenital Amaurosis
MLMT: Multi-Luminance Mobility Testing
FST: Full-field Light Sensitivity Testing
RPE65: Retinal Pigment Epithelium 65
VA: Visual Acuity

APPENDIX B: Therapeutic Alternatives

- Not Applicable.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None Reported.

- Boxed Warning(s):
  - 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 non-invasive 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's congenital amaurosis and other forms of autosomal recessive RP, which are characterized by early-onset blindness. Leber's 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.

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated. 2. Dosing information was updated to accompany updated indications. 3. Continued therapy criteria II.A.1 was rephrased to “Currently receiving medication that has been authorized by RxAdvance…”. 4. References were updated.	07/13/2020	09/14/2020
Policy was reviewed: 1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Initial Approval Criteria and Continued Therapy Approval Criteria was updated to remove HIM approval duration. 3. Initial Approval Criteria I.A.2 was updated to include ”or retinal surgeon	06/01/2021	09/14/2021

with experience providing sub-retinal injections…” 4. Appendix A was updated to include FST, RPE65 and VA. 5. References were reviewed and updated.		