Drug Monograph

Drug/Drug Class:	**Luxturna® (voretigene neparvovec-rzyl) suspension for subretinal injection/ Gene Therapy**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Luxturna® is a suspension for subretinal injection, supplied in a 0.5 ml extractable volume in a 2 ml single dose vial; the supplied concentration requires a 1:10 dilution prior to administration. Spark Pharmaceutics, Inc., Philadelphia, PA 19104
Summary of Findings:	Efficacy of Luxturna® was demonstrated in a randomized, open-label, phase 3 clinical trial. Patients receiving Luxturna® displayed a median score change of 2 on the multi-luminance mobility testing (MLMT) compared to a score change of 0 in the control group. In a secondary measure, analysis of white light full-field light sensitivity threshold (FST) testing showed statistically significant improvement from baseline to year 1 in the Luxturna treatment group compared to the control group.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Previously untreatable, RPE65-mediated inherited retinal dystrophy is an inherited retinal disease (IRD), and a natural history study has shown that people with it eventually progress to total blindness. People living with IRDs due to biallelic RPE65 gene mutations frequently suffer from night blindness as a result of decreased light sensitivity during childhood or early adulthood, as well as involuntary back and forth eye movements.

Dosage Form(s) [1]

Luxturna® is a suspension for subretinal injection, supplied in a 0.5 ml extractable volume in a 2 ml single dose vial; the supplied concentration requires a 1:10 dilution prior to administration.

Manufacturer [1]

Spark Pharmaceutics, Inc., Philadelphia, PA 19104

Indication(s) [1]

Luxturna® is an adeno-associated virus vector-based gene therapy 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).

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Luxturna® is designed to deliver a normal copy of the gene encoding the human retinal pigment epithelial 65 kDa protein (RPE65) to cells of the retina in persons with reduced or absent levels of biologically active RPE65. The RPE65 is produced in the retinal pigment epithelial cells and converts all-trans-retinol to 11 cis-retinol, which subsequently forms the chomophore, 11-cis-retinal, during the visual cycle. The visual cycle is critical in phototransduction, which refers to the biological conversion of a photon of light into an electrical signal in the retina. Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 isomerohydrolase activity, blocking the visual cycle and resulting in impairment of vision.

Pharmacokinetics:

Luxturna® vector DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction assay. The highest levels of vector DNA sequences were detected in intraocular fluids of vector-injected eyes. Low levels of vector DNA sequences were detected in the optic nerve of the vector-injected eye, optic chiasm, spleen and liver, and sporadically in the lymph nodes.

STUDY DESIGN	Phase 3, Open label, two-center, randomized clinical trial (n=31).
INCLUSION CRITERIA	Pediatric and adult patients with biallelic RPE65 mutation-associated retinal dystrophy.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive either subretinal injection of Luxturna® (n=21) or control (n=10). Patients who were randomized to the control group were crossed over to receive subretinal injection of Luxturna® after one year of observation.
RESULTS	Efficacy was established on the basis of multi-luminance mobility testing (MLMT) score change from baseline to year 1. The MLMT was designed to measure changes in functional vision, as assessed by the ability of a subject to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. A positive MLMT score (range of 0 to 6) change from baseline to year 1 visit indicated that the subject was able to complete the MLMT at a lower light level. The median MLMT score change for bilateral eyes was 2 for the Luxturna group compared to 0 in the control group. The median MLMT score change for the first-treated eye was 2 for the Luxturna group compared to 0 in the control group.
SAFETY	The most common adverse reactions were conjunctival hyperemia, cataract, increase intraocular pressure, retinal tear, dellen, macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- Endophthalmitis may occur following any intraocular surgical procedure or injection
- Permanent declined in visual acuity may occur following subretinal injection of Luxturna®
- Retinal abnormalities may occur during or following the subretinal injection of Luxturna®
- Increased intraocular pressure may occur after subretinal injection
- Instruction patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration has completely dissipated from the eye

- Subretinal injection of Luxturna® is associated with an increased incidence of cataract development and/or progression

Adverse Effects (1)

Most common, ≥ 5%	Subjects (n=41)	Treated Eyes (n=81)
Any ocular adverse reaction	66%	57%
Conjunctival hyperemia	22%	11%
Cataract	20%	19%
Increased intraocular pressure	15%	10%
Retinal tear	10%	5%
Dellen	7%	4%
Macular hole	7%	4%
Subretinal deposits	7%	4%
Eye inflammation	5%	5%
Eye irritation	5%	2%
Eye pain	5%	2%
Maculopathy	5%	4%

Drug Interactions (1)

- None listed

Dosage and Administration (1)

The recommended dose for each eye is 1.5×10^{11} vector genomes, administered by subretinal injection in a total volume of 0.3ml. Perform subretinal administration of Luxturna® to each eye on separate days within a close interval, but no fewer than 6 days apart.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	COST/ TREATMENT**
Voretigene neparvovec-rzyl	Luxturna	Spark	$846,600

** Maximum Allowable Cost

Conclusion

Luxturna® is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Luxturna® is a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the human RPE65 gene. It is the first FDA-approved gene therapy for a genetic disease, the first and only pharmacologic treatment for an inherited retinal disease and the first adeno-associated virus vector gene therapy approved in the U.S. In a phase 3 clinical trial, patients receiving Luxturna had a MLMT score change of 2, compared to a score change of 0 in patients receiving the control. Luxturna is a one-time treatment that costs approximately $846,700.

Recommendation

The Division recommends adding this drug as a Clinical Edit.

References

1) Luxturna. Retrieved 05/29/2018 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=08313a24-e7ce-457a-bb3f-161bc45517ee&audience=consumer
2) Shanley, Mathew. Spark Therapeutics' Luxturna Granted FDA Rare Pediatric Disease Designation. Retrieved 5/29/2018 from http://www.raredr.com/news/luxturna-rare-pediatric-disease-designation

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