LUXTURNA™ (VORETIGENE NEPARVOVEC-RZYL)

Policy Number: PHARMACY 305.4 T2 **Effective Date**: January 1, 2019

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Related Policy

- Review at Launch for New to Market Medications

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	Medical Benefit
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes[1]
Precertification with Medical Director Review Required	Yes[1]
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All
Special Considerations	[1]Precertification with review by a Medical Director or their designee is required.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The ember specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to: Acquired Rare Disease Drug Therapy Exception Process.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Luxturna is proven and/or medically necessary for the treatment of Inherited Retinal Dystrophies (IRD) caused by mutations in the retinal pigment epithelium-specific protein 65kDa (RPE65) gene in patients who meet ALL of the following criteria:[1-2]

- Patient is greater than 12 months of age; **and**
- Diagnosis of a confirmed biallelic RPE65 mutation-associated retinal dystrophy (e.g. Leber's congenital amaurosis [LCA], Retinitis pigmentosa [RP] Early Onset Severe Retinal Dystrophy [EOSRD], etc.); **and**
- Genetic testing documenting biallelic mutations of the RPE65 gene; **and**
- Sufficient viable retinal cells as determined by optical coherence tomography (OCT) confirming an area of retina within the posterior pole of >100 µm thickness; **and**
- Prescribed and administered by ophthalmologist or retinal surgeon with experience providing sub-retinal injections; **and**
- Patient has not previously received RPE65 gene therapy in intended eye.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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). Treatment with Luxturna 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.[3]

BACKGROUND

Leber's congenital amaurosis (LCA) and autosomal recessive retinitis pigmentosa (RP) are a group of inherited, early-onset, severe retinal dystrophies that cause substantial sight impairment in childhood. One of the causes of these conditions is mutations in the gene encoding RPE65 (retinal pigment epithelium–specific protein 65 kDa). Biallelic mutations in the RPE65 gene account for approximately 16% of cases of LCA and 2% of cases of recessive RP. The encoded retinoid isomerase converts all-trans retinyl esters to 11-cis retinal for the regeneration of visual pigment after exposure to light. RPE65 deficiency causes photoreceptor- cell dysfunction and impaired vision from birth. Severe dysfunction of rod photoreceptor cells, which are wholly reliant on retinal pigment epithelium–derived RPE65, causes severely impaired night vision. The function of cone photoreceptor cells, which mediate vision in daylight, is relatively preserved in childhood because cones have access to an alternative source of 11-cis retinal. However, progressive degeneration of both rod and cone photoreceptor cells, in association with local accumulation of toxic retinyl esters, results in severe sight impairment by early adulthood.[4-6]

Augmentation of RPE65 in animal models of RPE65 deficiency can improve retinal and visual function, as assessed by means of electroretinography (ERG) and observation of vision-guided behavior, respectively.[4-6] Since the target retinal cells are post mitotic cells, it is expected that a one-time administration of the gene product will provide benefit as long as the retina cells are viable. Gene therapy treatment does not produce new tissue so it is vital the patient have sufficient viable retinal cells prior to administration. This can be measured by optical coherence testing (OCT) documenting a retinal layer $\geq$100µm thick. [8]

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

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

ICD-10 Diagnosis Code	Description
H35.50	Unspecified hereditary retinal dystrophy
H35.52	Pigmentary retinal dystrophy
H35.54	Dystrophies primarily involving the retinal pigment epithelium

CLINICAL EVIDENCE

Phase 1 trials, done at the Children's Hospital of Philadelphia, showed safe and stable improvement in retinal and visual function in all 12 participants. These individuals received unilateral, subretinal injections of AAV2-hRPE65v2 (voretigene neparvovec) in their worse-seeing, non-preferred eye in a dose-escalation study, with doses from $1{\cdot}5 \times 10^{10}$ to $1{\cdot}5 \times 10^{11}$ vector genomes (vg). Most of these participants showed improved light sensitivity, navigational abilities, or visual acuity. A follow-on study, in which 11 of these 12 participants underwent injection of the contralateral eye at the dose of $1{\cdot}5 \times 10^{11}$ vg, demonstrated the safety of contralateral eye injection, as well as gains in visual and retinal function in the second eye. This improvement has remained durable over at least 3 years, with observation ongoing.

An open-label randomized controlled Phase 3 study in which subjects with confirmed biallelic RPE65 mutations were randomized in a 2:1 fashion to either the voretigene neparvovec group or control group and followed for one year. After completion of one year of observation, Control subjects were allowed to crossover and receive voretigene neparvovec treatment. Enrollment criteria include the following: subjects had to be at least three years of age with confirmed biallelic RPE65 mutations, subjects had to have a visual acuity of worse than or equal to 20/60 (for both eyes) and/or visual field of less than 20 degrees in any meridian as measured by a GVF III4e isopter or equivalent (both eyes), subjects had to have sufficient viable retinal cells as determined by non-invasive means, such as OCT (defined as an area of retina within the posterior pole of > 100 microns thickness) or ophthalmoscopy, subjects had to have the ability to comprehend the MLMT, follow course instructions, and the capacity to successfully navigate the course, and subjects had to have a baseline score on the MLMT that would allow a measurable improvement to be observed. The pre-specified primary efficacy endpoint was the change from Baseline at Year 1 in multi-luminance mobility test (MLMT) performance using the bilateral testing condition of the intervention group compared to controls. A total of 29 subjects were randomized and received intervention, 20 to the intervention arm and 9 to control. Overall, 72% of all treated subjects (21 of 29) achieved the maximum possible MLMT improvement one-year post-administration, demonstrating significant improvement in functional vision at lower light levels. The benefits observed at one year in the original intervention group continued through at least two years post-administration, with observation ongoing.[3,9,10]

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. *[2018D0063A*]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	• Updated list of applicable HCPCS codes: ○ Added J3398* ○ Removed C9032*, J3490, and J3590 *(*annual code edit)* • Archived previous policy version PHARMACY 305.3 T2