BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

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LUXTURNA™ (voretigene neparovec-rzyl)

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

LUXTURNA (voretigene neparovec-rzyl) (cont.)

Description:

Luxturna (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of individuals with confirmed biallelic RPE65 variant-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.

Biallelic RPE65 variant-associated retinal dystrophy, is a rare genetic condition. It is one of several eye conditions that result from genetic variants in a set of about 220 genes that control for retinal pigment epithelium-specific 65 kDa protein (RPE65, also known as retinoid isomerohydrolase). Individuals with biallelic variants have difficulty seeing in dim light and have progressive loss of vision.

The RPE65 gene provides instructions for making an enzyme that is essential for normal vision. Variants in the gene lead to reduced or absent levels of RPE65 activity, blocking the visual cycle and resulting in impaired vision. Individuals with biallelic RPE65 variant-associated retinal dystrophy experience a slowly progressive deterioration of vision over time. RPE65-mediated retinal disease starts with rod photoreceptors and later progresses to the cone photoreceptors in the macula. Dysfunction of rod photoreceptor cells, which are solely reliant on RPE65, causes severely impaired night vision. The function of cone photoreceptor cells, which mediate vision in daylight, are relatively preserved. The deterioration of vision, often during childhood or adolescence, ultimately progresses to complete blindness. Most become completely blind by young adulthood.

A number of inherited retinal diseases are caused by recessive variants in the RPE65 gene that codes for the protein RPE65. Variants that affect both copies of the RPE65 gene cause Leber Congenital Amaurosis, type 2 (LCA2), Early Onset Severe Retinal Dystrophy (EOSRD), Severe Early Childhood-onset Retinal Dystrophy (SECORD), Retinitis Pigmentosa type 20 (RP20) and other phenotypes.

Luxturna works by delivering a normal copy of the RPE65 gene directly to viable retinal cells using gene therapy with an adeno-associated virus vector that expresses RPE65. Individuals must have viable retinal cells. The viral vector transfers intact copies of the RPE65 gene directly behind the retina. The retinal cells then produce the normal protein that converts light to an electrical signal in the retina to restore the individual's vision loss.

LUXTURNA (voretigene neparovec-rzyl) (cont.)

Description: (cont.)

Genetic Testing to Diagnose Biallelic RPE65-Mediated Inherited Retinal Dystrophies:

Genetic testing is required to identify the presence of pathogenic or likely pathogenic variants in the RPE65 gene.

Pathogenic and likely pathogenic variant(s) must be present in both copies of the RPE65 gene to establish a diagnosis of biallelic RPE65-mediated inherited retinal dystrophy.

A single RPE65 pathogenic or likely pathogenic variant found in the homozygous state (e.g., the presence of the same variant in both copies alleles of the RPE65 gene) establishes a diagnosis of biallelic RPE65-mediated dystrophinopathy.

However, if 2 different RPE65 pathogenic or likely pathogenic variants are detected (e.g., compound heterogygous state), confirmatory testing is required to determine the *trans vs cis* configuration (e.g., whether the 2 different pathogenic or likely pathogenic variants are found in different copies or in the same copy of the RPE65 gene).

The presence of 2 different RPE65 pathogenic or likely pathogenic variants in separate copies of the RPE65 gene (*trans* configuration) establishes a diagnosis of biallelic RPE65-mediated dystrophinopathy.

The presence of 2 different RPE65 pathogenic or likely pathogenic variants in only 1 copy of the RPE65 gene (cis configuration) is not considered a biallelic RPE65-mediated dystrophinopathy.

LUXTURNA (voretigene neparovec-rzyl) (cont.)

Criteria:

Luxturna will be reviewed by the medical director(s) and clinical pharmacist(s).

See Resources section for FDA-approved dosage.

- Luxturna sub-retinal injection for individuals with vision loss due to biallelic RPE65 variant-associated retinal dystrophy is considered ***medically necessary*** with documentation of **ALL** of the following:

1. Request is from a provider who is a retinal specialist with expertise in vitreoretinal surgery
2. Surgery to be performed in an approved specialized facility with an active ophthalmology practice treating individuals with retinal dystrophies
3. Individual is 12 months of age or older
4. **ALL** of the following:

   - Genetic testing has confirmed presence of **ONE** of the following bilallelic RPE65 pathogenic or likely pathogenic variant(s):

     a. RPE65 pathogenic or likely pathogenic variant found in the homozygous state
     b. RPE65 pathogenic or likely pathogenic variants found in the trans configuration (compound heterozygous state) by segregation analysis

   - Presence of viable retinal cells as assessed by optical coherence tomography imaging and/or ophthalmoscopy with **ONE** of the following:

     a. An area of retina within the posterior pole of > 100 µm thickness shown on optical coherence tomography
     b. ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole based on ophthalmoscopy
     c. Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent

LUXTURNA (voretigene neparovec-rzyl) (cont.)

Criteria: (cont.)

- Luxturna sub-retinal injection for individuals with vision loss due to biallelic RPE65 variant-associated retinal dystrophy is considered ***medically necessary*** with documentation of **ALL** of the following: (cont.)

  5. Individual does not have **ANY** of the following:

     - Woman of childbearing potential who is pregnant or unwilling to use effective contraception for 4 months following administration of Luxturna
     - Woman who is breast feeding an infant or child
     - Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme, unless they have been discontinued for 18 months
     - Prior intraocular surgery within the last 6 months
     - Preexisting eye conditions or complicating systemic diseases that would preclude planned surgery or interfere with the efficacy of therapy, including, *but not limited to*:

       a. Malignancies whose treatment could affect central nervous system function (e.g., radiotherapy of the orbit; leukemia with central nervous system/optic nerve involvement)
       b. Individuals with diabetes or sickle cell disease if they have any manifestation of advanced retinopathy (e.g., macular edema, proliferative changes)
       c. Individuals with immunodeficiency (acquired or congenital) who could be susceptible to opportunistic infection (e.g., cytomegalovirus retinitis)

- Luxturna for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Treatment with dosing or frequency outside the FDA-approved dosing and frequency

LUXTURNA (voretigene neparovec-rzyl) (cont.)

Resources:

Literature reviewed 06/26/18. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

1. 2.04.144 BCBS Association Medical Policy Reference Manual. Gene Therapy for Inherited Retinal Dystrophy. Issue date 01/11/2018.

Luxturna Package Insert:

- FDA-approved indication and dosage:

Indication	Recommended Dose
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).	The recommended dose of LUXTURNA for each eye is 1.5 x 1011 vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL. Perform subretinal administration of LUXTURNA to each eye on separate days within a close interval, but no fewer than 6 days apart. Recommend systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of LUXTURNA to each eye), and followed by a tapering dose during the next 10 days.

Initial Approval Duration:
Once in a life-time

LUXTURNA (voretigene neparovec-rzyl) (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nílínigíí Blue Cross Blue Shield of Arizona haada yit'éego bína'ídíłkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'ídíłkidgo beehaz'áanii hóló díí t'áá hazaadk'ehjí háká a'doowołgo bee haz'ą doo bąąh íłínígóó. Ata' halne'ígíí kojį' bich'į' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون اية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.

LUXTURNA (voretigene neparovec-rzyl) (cont.)

<u>Multi-Language Interpreter Services</u>: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi:
اگر شما، یا کسی که شما به او کمک میکنید ، سوال در مورد Blue Cross Blue Shield of Arizona ، داشته باشید حق این را دارید که کمک و
اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799
.[تماس حاصل نمایید

Assyrian:
[illegible] Blue Cross Blue Shield of Arizona [illegible]
[illegible] 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคณ หรอคนทคณกาลงชวยเหลอมคาถามเกยวกบ Blue Cross Blue Shield of Arizona
คณมสทธทจะไดรบความชวยเหลอและขอมลในภาษา ของคณไดโดยไมมคาใชจาย พดคยกบลาม โทร 877-475-4799