LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

LUXTURNA REIMBURSEMENT GUIDE FOR TREATMENT CENTERS

LUXTURNA® (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

Spark® Therapeutics is committed to working with you and providing detailed information to assist in reimbursement for LUXTURNA and related support services.

This guide was created to provide information to Treatment Centers to help with the reimbursement process for LUXTURNA.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

Indication

LUXTURNA (voretigene neparvovec-rzyl) 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 physicians.

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, chorioretinal atrophy, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity

Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use

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 the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see here for the US Full Prescribing Information for LUXTURNA.

CONTENTS

Select any of the items below to go to the corresponding section.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

OVERVIEW OF THE PATIENT JOURNEY WITH LUXTURNA® (VORETIGENE NEPARVOVEC-RZYL)

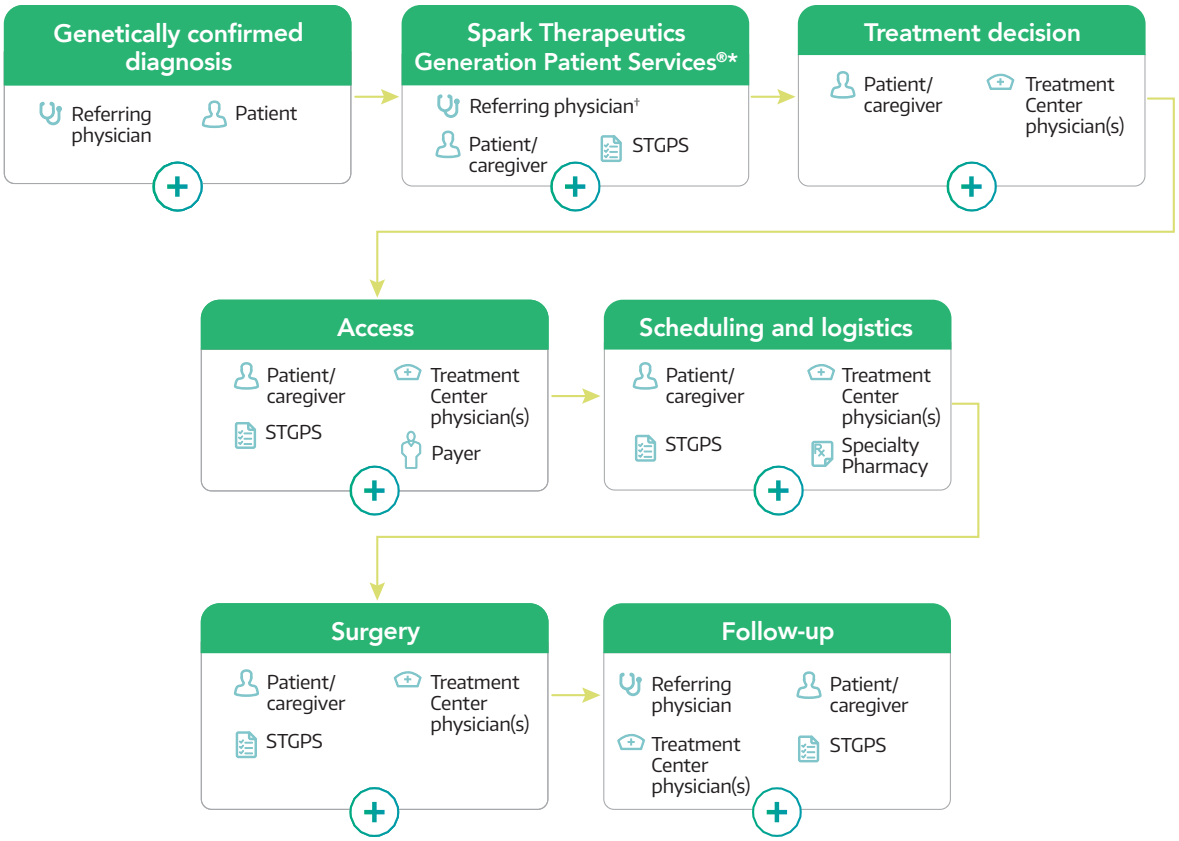
Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Outline of the patient journey with LUXTURNA® (voretigene neparvovec-rzyl)

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

While each patient who receives LUXTURNA experiences his or her own distinct treatment journey, the outline below can help when working with your enrolled patients and their caregivers.



STGPS=Spark Therapeutics Generation Patient Services.

*Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on your patients' ability to get treatment or the nature of your patients' treatment or care. Generation Patient Services does not provide medical advice.

†Referring physician is not required for enrollment into Spark Therapeutics Generation Patient Services.

Work with Spark Therapeutics Generation Patient Services to help coordinate coverage and care for your enrolled patients.

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

LUXTURNA® voretigene neparvovec-rzyl for subretinal injection

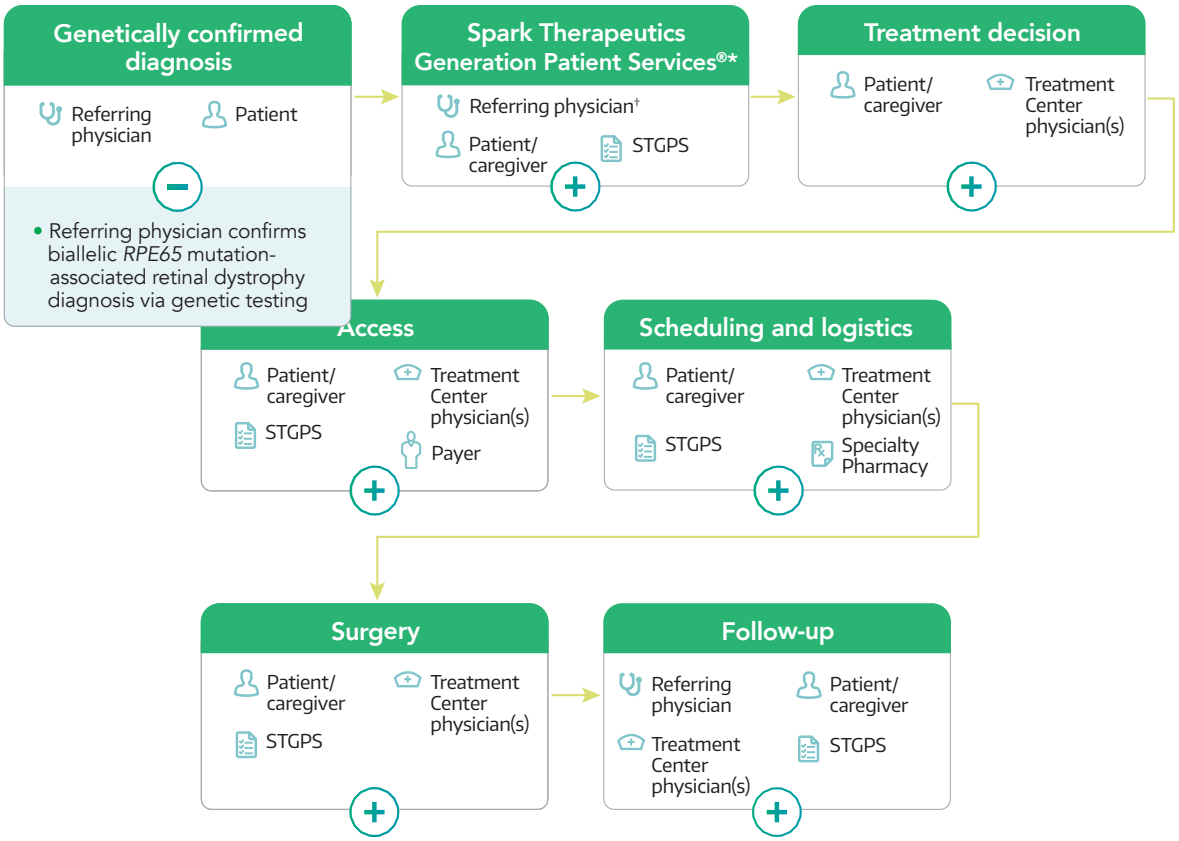
Patient Journey
Support Team
Patient Consultations
Benefits Investigation
Financial Assistance
Ordering and Distribution
Coding and Claims
Appendix

Outline of the patient journey with LUXTURNA® (voretigene neparvovec-rzyl)

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

While each patient who receives LUXTURNA experiences his or her own distinct treatment journey, the outline below can help when working with your enrolled patients and their caregivers.



STGPS=Spark Therapeutics Generation Patient Services.

*Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on your patients' ability to get treatment or the nature of your patients' treatment or care. Generation Patient Services does not provide medical advice.

†Referring physician is not required for enrollment into Spark Therapeutics Generation Patient Services.

Work with Spark Therapeutics Generation Patient Services to help coordinate coverage and care for your enrolled patients.

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

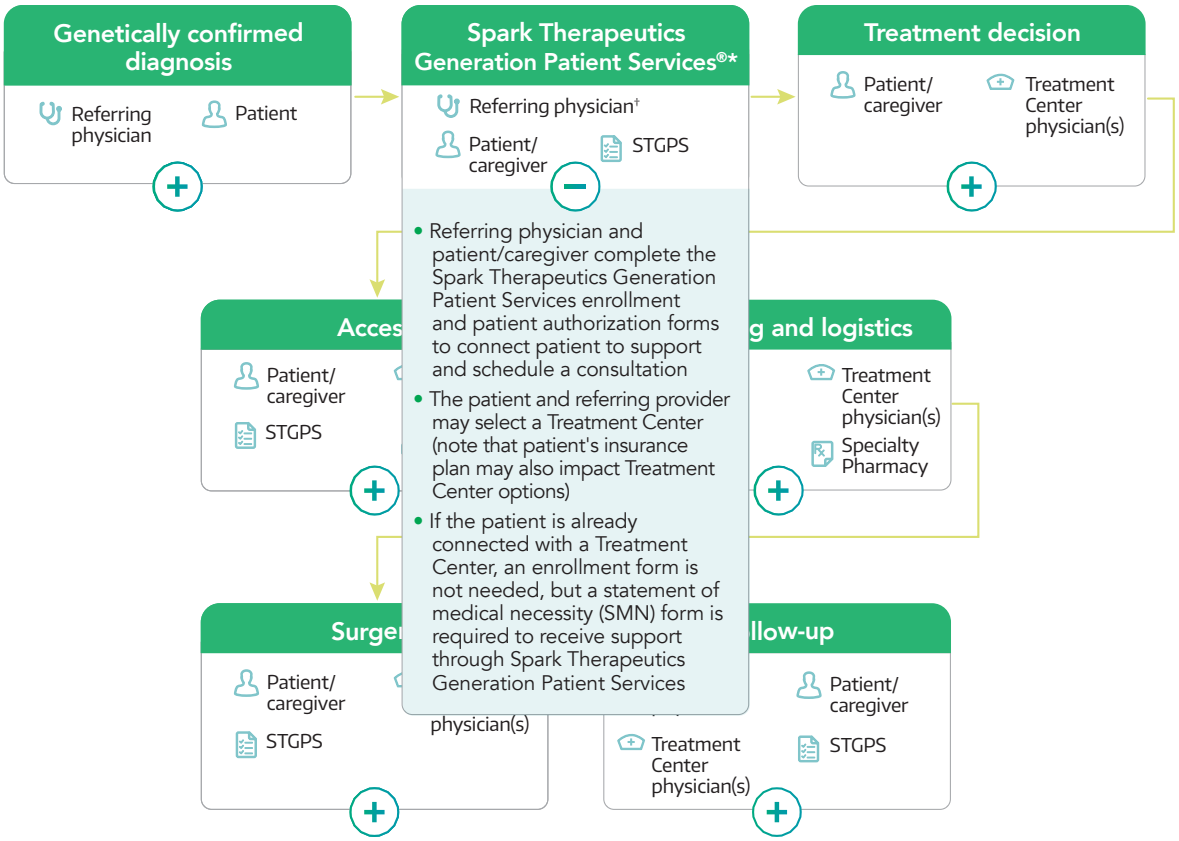
LUXTURNA® voretigene neparvovec-rzyl for subretinal injection

Outline of the patient journey with LUXTURNA® (voretigene neparvovec-rzyl)

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

While each patient who receives LUXTURNA experiences his or her own distinct treatment journey, the outline below can help when working with your enrolled patients and their caregivers.



STGPS=Spark Therapeutics Generation Patient Services.

*Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on your patients' ability to get treatment or the nature of your patients' treatment or care. Generation Patient Services does not provide medical advice.

†Referring physician is not required for enrollment into Spark Therapeutics Generation Patient Services.

Work with Spark Therapeutics Generation Patient Services to help coordinate coverage and care for your enrolled patients.

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

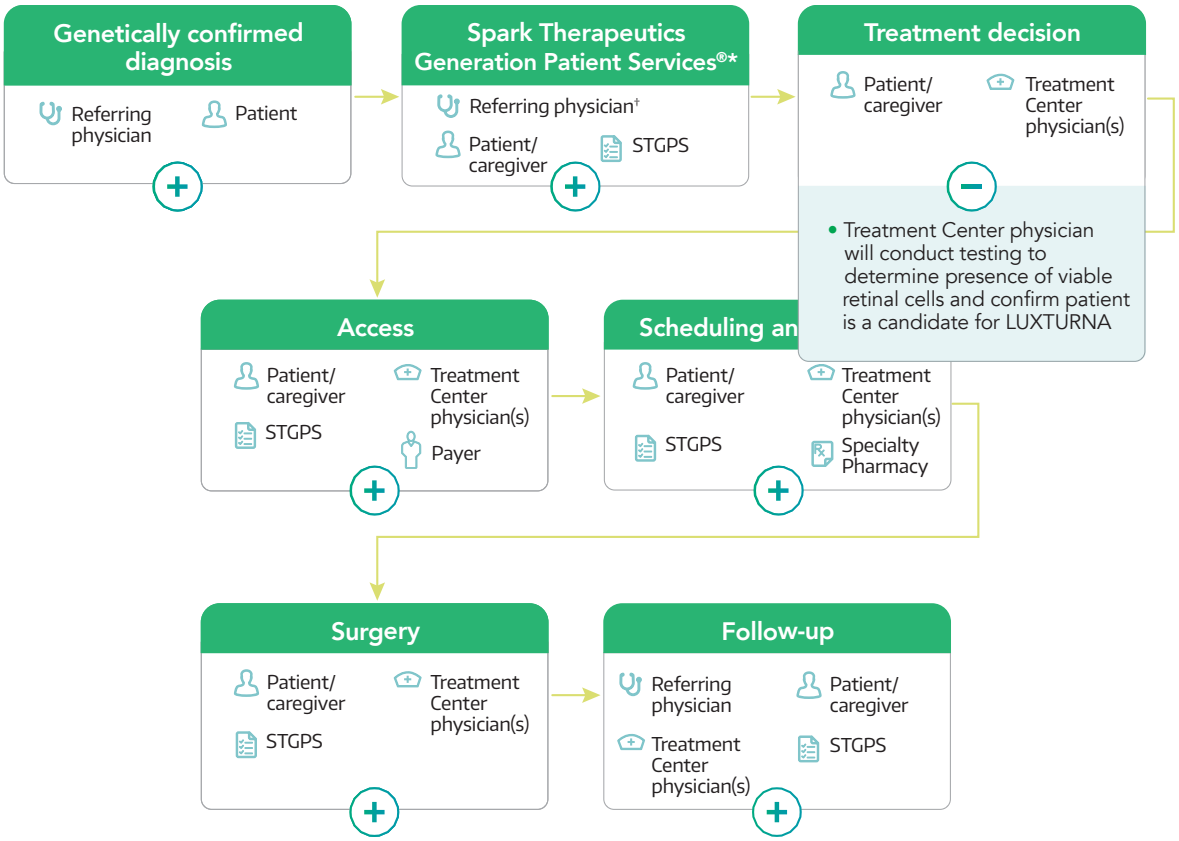
LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

Outline of the patient journey with LUXTURNA® (voretigene neparvovec-rzyl)

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

While each patient who receives LUXTURNA experiences his or her own distinct treatment journey, the outline below can help when working with your enrolled patients and their caregivers.



STGPS=Spark Therapeutics Generation Patient Services.

*Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on your patients' ability to get treatment or the nature of your patients' treatment or care. Generation Patient Services does not provide medical advice.

†Referring physician is not required for enrollment into Spark Therapeutics Generation Patient Services.

Work with Spark Therapeutics Generation Patient Services to help coordinate coverage and care for your enrolled patients.

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

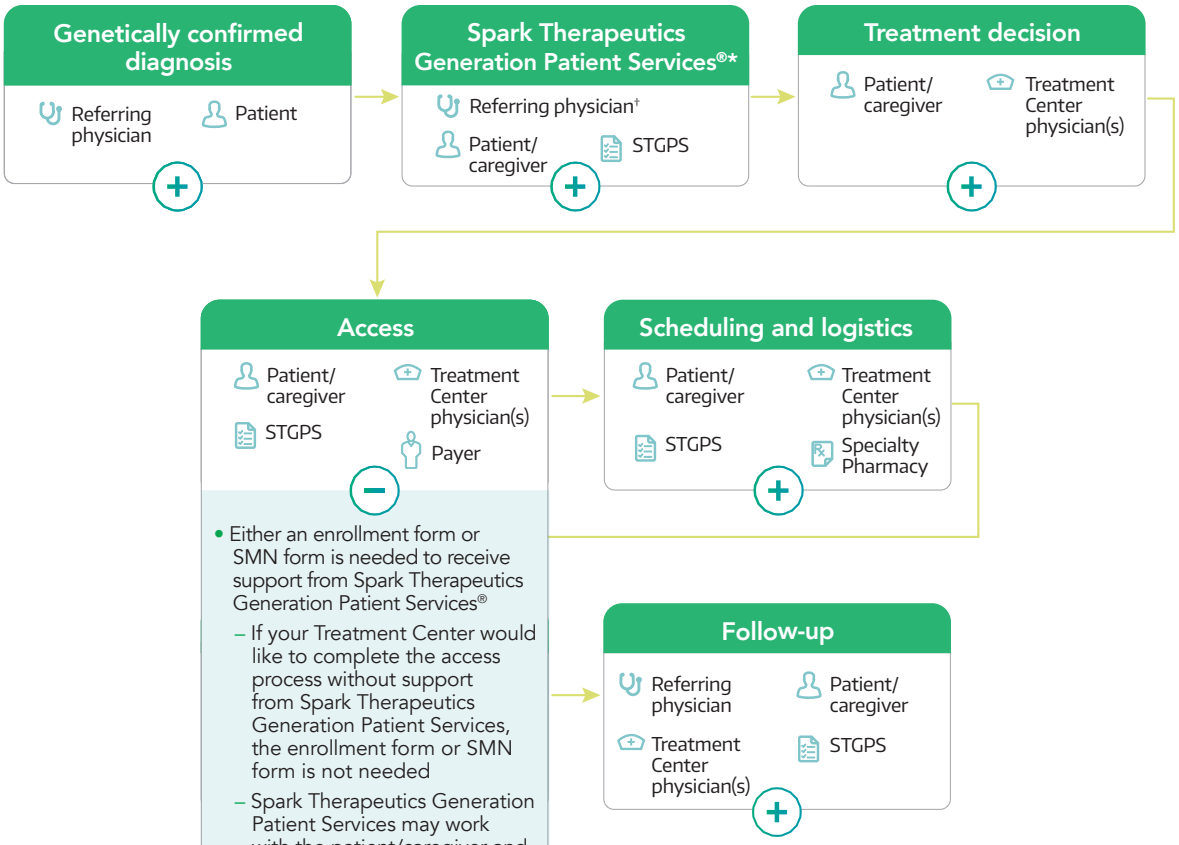
Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

Outline of the patient journey with LUXTURNA® (voretigene neparvovec-rzyl)

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

While each patient who receives LUXTURNA experiences his or her own distinct treatment journey, the outline below can help when working with your enrolled patients and their caregivers.



STGPS=Spark Therap

*Participation in Spark vices is voluntary. Patients may choose to participate in all, some, or none of the services to participate in these services will have no effect on your patients' ability to get treatme atment or care. Generation Patient Services does not provide medical advice.

†Referring physician is not required for enrollment into Spark Therapeutics Generation Patient Services.

Work with Spark Therapeutics Generation Patient Services to help coordinate coverage and care for your enrolled patients.

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

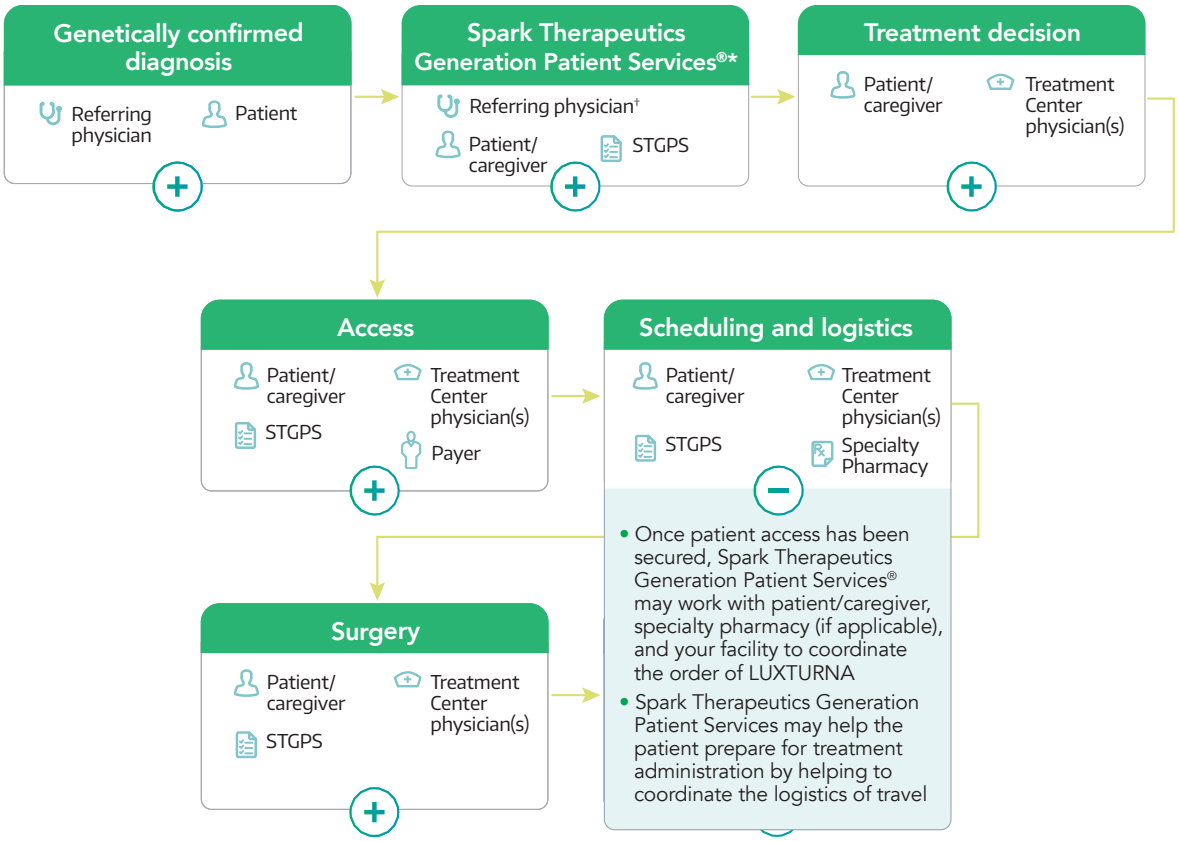
Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

Outline of the patient journey with LUXTURNA® (voretigene neparvovec-rzyl)

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

While each patient who receives LUXTURNA experiences his or her own distinct treatment journey, the outline below can help when working with your enrolled patients and their caregivers.



STGPS=Spark Therapeutics Generation Patient Services.

*Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on your patients' ability to get treatment or the nature of your patients' treatment or care. Generation Patient Services does not provide medical advice.

†Referring physician is not required for enrollment into Spark Therapeutics Generation Patient Services.

Work with Spark Therapeutics Generation Patient Services to help coordinate coverage and care for your enrolled patients.

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

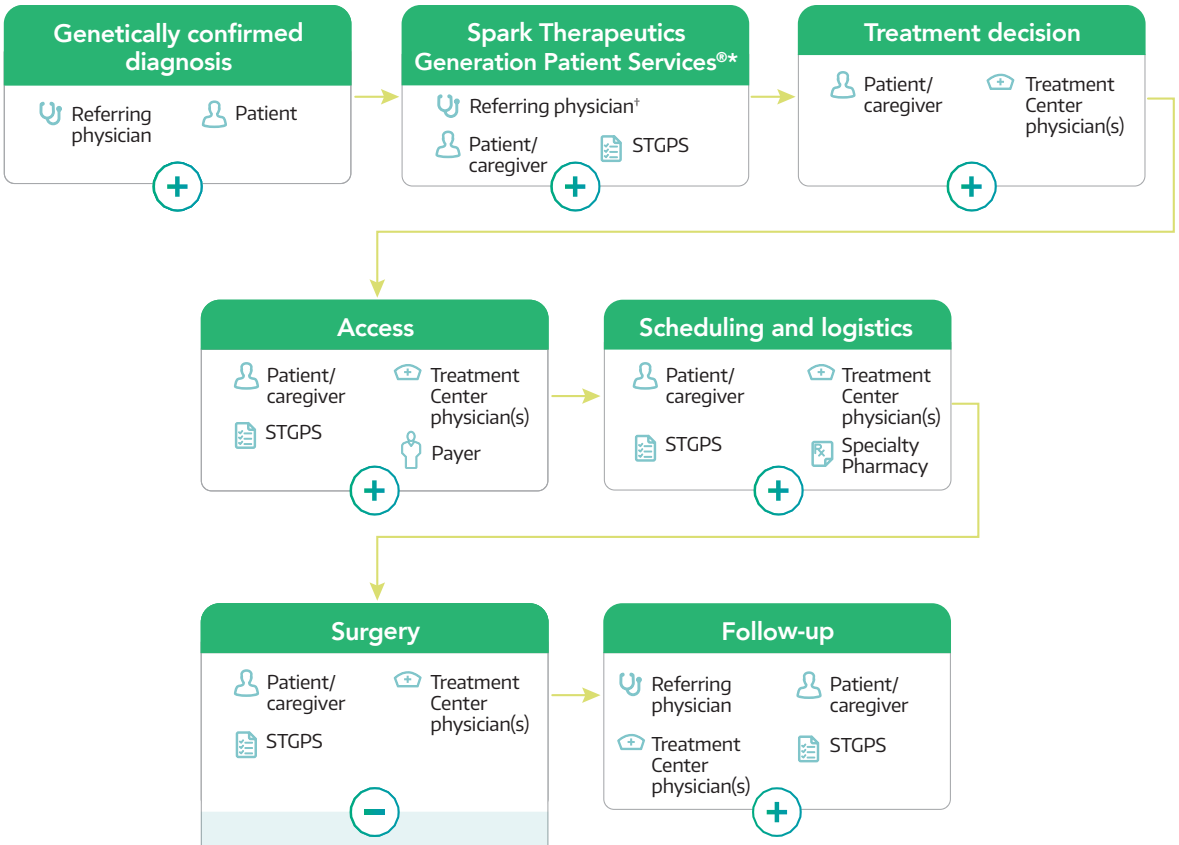
Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

Outline of the patient journey with LUXTURNA® (voretigene neparvovec-rzyl)

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

While each patient who receives LUXTURNA experiences his or her own distinct treatment journey, the outline below can help when working with your enrolled patients and their caregivers.



- Once the patient is at your facility, the Treatment Center surgeon leads administration of LUXTURNA for the first eye
- Spark Therapeutics Generation Patient Services® may help coordinate patient/caregiver/ family accommodations during the interval between treatment administration of first and second eyes
- Within a close interval, but no fewer than 6 days apart, the surgeon leads administration of LUXTURNA for the second eye[1]

STGPS=Spark Therap

*Participation in Spark vices is voluntary. Patients may choose to participate in all, some, or none of the services to participate in these services will have no effect on your patients' ability to get treatme atment or care. Generation Patient Services does not provide medical advice.

†Referring physician is rk Therapeutics Generation Patient Services.

Work with Spark atient Services to help coordinate coverage and care for you

Important Safet

Warnings and Pr

- **Endophthalmit** raocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

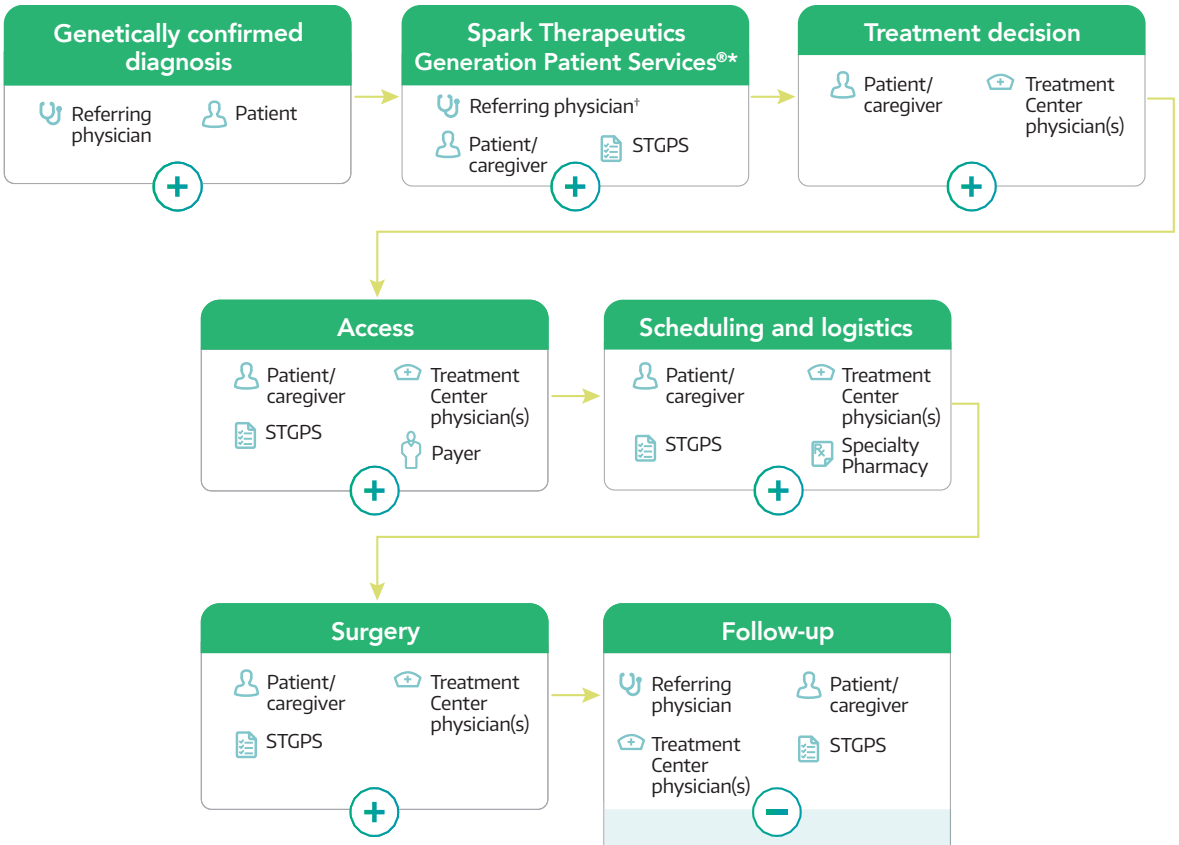
Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

Outline of the patient journey with LUXTURNA® (voretigene neparvovec-rzyl)

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.[1]

Patients must have viable retinal cells as determined by the treating physicians.[1]

While each patient who receives LUXTURNA experiences his or her own distinct treatment journey, the outline below can help when working with your enrolled patients and their caregivers.



STGPS=Spark Therapeutics Generation Patient Services.

*Participation in Spark Therapeutics Generation Patient Services [illegible] participate in all, some, or none of the services offered. Participating or deciding not to pa[illegible] effect on your patients' ability to get treatment or the nature of your patients' treatmen[illegible]s does not provide medical advice.

†Referring physician is not required for enrollment into Spark The[illegible]s.

Work with Spark Therapeutics Generation Patie[illegible]te coverage and care for your enrolled patients.

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Reference: 1. LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

INTRODUCING SPARK THERAPEUTICS GENERATION PATIENT SERVICES®

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Spark Therapeutics Generation Patient Services® offers dedicated support that's customized for your patients

Spark Therapeutics Generation Patient Services can help you and your enrolled patients and their caregivers understand the coverage process, work with insurance companies, access financial assistance, and receive resources and support as needed.

Spark Therapeutics Generation Patient Services overview

Spark Therapeutics Generation Patient Services can support your enrolled patients by:

- Providing a caring support team for patients/caregivers from confirmed diagnosis through post-surgery follow-up
- Helping to navigate insurance coverage, and connecting your patients with financial assistance resources as needed and available
- Facilitating the logistics of your patients' Treatment Center visits
- Answering any nonmedical questions your patients may have along the way
- Assisting patients with travel logistics and planning, and connecting them and their caregivers to resources that can provide support during the treatment process
  - Because of legal requirements, some services and resources are not available to patients with government insurance

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Enrolling in Spark Therapeutics Generation Patient Services®

To enroll in Spark Therapeutics Generation Patient Services,* patients must complete an enrollment form or complete the Authorization and Disclosure section within the statement of medical necessity (SMN) form that is initiated by the treating provider. While the program is optional, we encourage patients to take advantage of this free service. Patients will also need to complete the Authorization to Use and Disclose Health Information.

Once patients are enrolled, Spark Therapeutics Generation Patient Services will help schedule a consultation at their designated Treatment Center. In each case, the Treatment Center will be identified based on the patient's insurance coverage, home location, and preferences.

If a patient is already at their designated Ocular Gene Therapy Treatment Center, an enrollment form is not necessary. In this case, an SMN form is needed instead. **Either an enrollment form or an SMN form is required to receive support from Spark Therapeutics Generation Patient Services.**

To contact Spark Therapeutics Generation Patient Services, you can:

Call toll-free:
1-833-SPARK-PS (1-833-772-7577)

Email
mysparkgeneration@sparktx.com

Fax
678-727-1501

*Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on your patients' ability to get treatment or the nature of your patients' treatment or care. Generation Patient Services does not provide medical advice.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

PATIENT REFERRALS AND CONSULTATIONS FOR TREATMENT CENTERS

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

An overview of patient referrals and consultations

Patient consultations at your facility will be required to establish whether a patient is a viable candidate for LUXTURNA® (voretigene neparvovec-rzyl). Patients will be referred to your facility by a referring provider after genetic testing is administered for consultation.

If a patient is referred by a provider outside of your facility, office staff at your Treatment Center may need to engage the referring provider's practice to support the patient with a consultation authorization. This is especially relevant when the patient does not have out-of-network coverage for consultations.

The following materials may be needed to assist with obtaining a patient consultation authorization:

- Genetic testing results
- Prior authorization form
- Chart notes on patient from referring physician

Please refer to Benefits Investigation (page 20) for more information.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Out-of-network and out-of-state patient referrals

Insurers may require consultation authorization in certain situations:

- Patients with private commercial insurance; payers may not cover services provided by nonpreferred providers or may associate those services with higher out-of-pocket costs
- Medicaid beneficiaries or patients with Managed Medicaid plans may have coverage that is limited to participating providers within their state
- Patients who are insured through a Health Maintenance Organization (HMO) plan, which may require referral authorization

Please refer to Benefits Investigation (page 20) for more information.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Checklist and considerations for establishing coverage

The patient's insurance plan may require the following information or documentation for Treatment Center consultation authorization:

- Chart notes and imaging by referring provider
- Letter or explanation of why patient must go out of network or state for consultation
  - For example, no Treatment Centers within their preferred network or state due to limited availability of facilities
- Treatment Center procedure codes
- Treatment Center facility name and tax ID
- Healthcare professional's name, address, phone number, and contact information

Considerations:

- Required materials for consultation authorization of potential LUXTURNA® (voretigene neparvovec-rzyl) treatment may vary by insurer
- The party submitting the request for approval of consultation may also vary by insurer; ie, facility, referring provider, or in-network primary care physician (PCP)

Please refer to Benefits Investigation (page 20) for more information.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

BENEFITS INVESTIGATION, PRIOR AUTHORIZATION, AND APPEALS

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Getting started with access

Each patient journey with LUXTURNA® (voretigene neparvovec-rzyl) is unique—and Spark Therapeutics Generation Patient Services® is here to help

Spark Therapeutics Generation Patient Services* may provide support and education on benefit investigation outcomes, prior authorization, and appeals process, if applicable.

To receive support throughout the access process, work with your patient and/or their caregiver to complete an enrollment form or SMN form

- The enrollment form or SMN form starts the Spark® Therapeutics benefits investigation process, including determining coverage status. The benefits investigation process will be initiated once patient is enrolled in Spark Therapeutics Generation Patient Services
- Once an enrollment form or SMN form has been received along with the Patient Authorization to Use and Disclose Health Information, your patient's Spark Therapeutics Generation Patient Services team will communicate the next steps
- Spark Therapeutics Generation Patient Services will confirm that there have been no changes and that coverage is in place

Please refer to the appendix or visit the Spark Therapeutics Generation Patient Services website for more information.

*Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on your patients' ability to get treatment or the nature of your patients' treatment or care. Generation Patient Services does not provide medical advice.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Prior authorization and required documentation

Info

- Prior authorization or pre-certification may be required for treatment with LUXTURNA® (voretigene neparvovec-rzyl)
- Each payer may have different requirements regarding the authorization process
- PCP or in-network referrals are required when a patient has an HMO or an out-of-network/out-of-state insurance plan
- Expand to see examples of authorization documentation and coverage parameters

Action

- When obtaining details on prior authorization, your facility may want to:
  - Determine if the information can be phoned in, faxed, emailed, or submitted through the insurer's website
  - Find out how long it will take for a decision to be made
  - Keep a copy of everything submitted that is relevant to the prior authorization
  - Log any calls your facility makes about the request and note the name of the person you spoke with
  - Follow up with payer if your facility does not receive notification of the decision in a timely manner
- During the prior authorization process, consider establishing whether additional prior authorization is required to approve administration services and site of care
- Insurance verification may be required if follow-up is requested by the inherited retinal disease specialist or surgeon beyond the typical post-operation appointment

Spark Therapeutics Generation Patient Services® is available to assist with understanding the prior authorization process.

Important Safety Information

Warnings and Precautions (cont'd)

- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, chorioretinal atrophy, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Prior authorization and required documentation

Info

- Prior authorization or pre-certification may be required for treatment with LUXTURNA® (voretigene neparvovec-rzyl)
- Each payer may have different requirements regarding the authorization process
- PCP or in-network referrals are required when a patient has an HMO or an out-of-network/out-of-state insurance plan
- Expand more to see examples of authorization documentation and coverage parameters

Identify specific documents that may need to be submitted with the request, such as:

Statement of medical necessity form
Chart notes or imaging
Genetic testing results (please see below)
Authorization number
Specific payer prior authorization form
LUXTURNA US Prescribing Information
Relevant literature, including previously published standards of care
Clinical documents related to the disease, including: • Diagnostic evidence of inherited retinal disease, such as genetic testing results • Clinical presentation and duration of the symptoms • Current supportive care management • Care plan • Other relevant aspects of patient history – **Note:** Each plan may require some or more of the above information for submission

Spark Therapeutics Generation Patient Services® is available to assist with understanding the prior authorization process.

Important Safety Information

Warnings and Precautions (cont'd)

- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, chorioretinal atrophy, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Potential provider network restrictions

Info

- Due to the limited number of Treatment Centers, patients who receive LUXTURNA® (voretigene neparvovec-rzyl) may face restrictions from their insurers because the surgeon and/or Treatment Center is out of network or out of state
- Each payer may have a network of participating providers who have agreed to provide care under specific terms:
  - For patients with private commercial insurance, payers may not cover services provided by nonpreferred providers or may associate those services with higher out-of-pocket costs
  - For Medicaid beneficiaries, coverage may be limited to participating in-state providers
  - For patients enrolled in Medicaid Managed Care who may only be able to receive care from in-network providers within their state
  - For patients insured through an HMO plan
- Payers may grant coverage exceptions if medical necessity is established, contingent on a consultation with the approved Treatment Center

Action

- For a patient to receive a waiver on grounds of medical necessity, your facility may want to:
  - Verify the state and/or network participation status of the physician(s) and/or your treatment facility
  - Determine and record the patient out-of-pocket costs for out-of-state/out-of-network providers
  - Find out if there is an exception process for patients seeking care out of state and/or out of network, and if this depends on whether the patient is covered through commercial or government insurance
- A consultation involving the patient, caregiver, referring physician, and Treatment Center may be necessary to facilitate the insurance approval process. For more information on patient consultations, please see page 16

Spark Therapeutics Generation Patient Services® can help your facility determine potential network restrictions and navigate this process.

Note: Ancillary services may not be in-network. Speak to your patients and their referring physicians to plan accordingly.

Important Safety Information

Warnings and Precautions (cont'd)

- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Coordination of benefits for multiple payers

Info

- Your patients eligible for LUXTURNA® (voretigene neparvovec-rzyl) may have multiple payers that provide benefit coverage (for example, a commercial health plan and Medicaid/Medicare)

Action

- During the benefits investigation process, your facility may want to establish which payer is primary, and which are secondary and tertiary (if applicable)
- After establishing the order of benefits, consider following the instructions from each payer on coordination of benefits for reimbursement/payment

Because the prior authorization process may not yet be defined for gene therapy, Spark Therapeutics Generation Patient Services® is available to work with you and your patients to determine next steps in the absence of process or policy.

Important Safety Information

Warnings and Precautions (cont'd)

- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Appealing a denial

If your patient's claim is denied, contact Spark Therapeutics Generation Patient Services® for assistance with the logistics of the appeals process

If your prior authorization request for LUXTURNA® (voretigene neparvovec-rzyl) is denied, you may be able to appeal. Appeals must adhere to each payer's requirements and include additional information that emphasize the medical necessity of LUXTURNA for the patient. Spark Therapeutics Generation Patient Services is available to walk your facility through the appeals process.

Suggested guidelines for how to appeal:

Determine the reason for the denial (eg, clerical, clinical, or benefit driven)

If the denial was for clerical reasons, consider immediately resubmitting the request with the proper information

- Clerical reasons claims may be denied:
  - Incorrect codes
  - Missing information
  - Incorrect product information

If the denial was for clinical reasons, consider evaluating what additional information may be required to demonstrate medical necessity

If the denial was for benefits reasons, consider calling the payer to determine if an exception to the benefit may be allowed and to determine the process for such an exception (for example, if LUXTURNA is not yet covered under the insurer's coverage benefit, or if the patient has no out-of-network benefits and Treatment Center is out of network)

Verify the appeals process for the payer

Record the correspondence with the payer at every point of the appeals process, including date, time, point of contact, and nature of discussion

If your appeal is denied again, work with Spark Therapeutics Generation Patient Services representatives to consider an external review

Important Safety Information

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

FINANCIAL ASSISTANCE OPTIONS FOR LUXTURNA® (VORETIGENE NEPARVOVEC-RZYL)

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Financial assistance options for LUXTURNA® (voretigene neparvovec-rzyl)

Your patients eligible for LUXTURNA have options for financial support based on their insurance type

- **Commercial insurance**
  - If your patients have commercial insurance without secondary/tertiary government insurance, Spark Therapeutics Generation Patient Services® offers a co-pay assistance program that may help with out-of-pocket costs

- **Government insurance**
  - If your patients have government insurance, Spark Therapeutics Generation Patient Services can refer them to independent nonprofit 501(c)(3) organizations that may be able to help with out-of-pocket costs

- **Uninsured or underinsured**
  - If your patient is uninsured or underinsured and has enrolled in Spark Therapeutics Generation Patient Services, Generation Patient Services can help them explore available insurance options

Spark Therapeutics Generation Patient Services can help connect enrolled patients to resources that may assist with out-of-pocket costs.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

ORDERING LUXTURNA® (VORETIGENE NEPARVOVEC-RZYL)

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Ordering and distribution processes for LUXTURNA® (voretigene neparvovec-rzyl) may vary from patient to patient

Ordering

- **Contact Spark® Therapeutics to initiate and coordinate the ordering process. Please note the following information may be required to help us support you with this*:**
  - Completed order form provided by Spark Therapeutics Generation Patient Services®
  - Treatment Center purchase order number and form
  - Copy of patient's approved prior authorization form

*This list is not all inclusive. It provides examples of documents that may be required based on insurance type and path. Patients do not need to enroll in Spark Therapeutics Generation Patient Services in order to receive treatment; other ordering methods are available.

Distribution

- **Spark Therapeutics offers innovative distribution choices for LUXTURNA**
  - We are committed to working with your Treatment Center, patients/caregivers, payers, and other key stakeholders to determine the best fit for you and your patients' needs
- **Contact Spark Therapeutics Generation Patient Services to learn more**

Spark Therapeutics Generation Patient Services is available to provide more information or facilitate the ordering and distribution processes.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

SUBMITTING CLAIMS FOR LUXTURNA® (VORETIGENE NEPARVOVEC-RZYL)

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Payer billing guidelines can facilitate claims processing and prompt payment

Coding

Different code sets are used in various sites of service. International Classification of Diseases, Tenth Revision (ICD-10) diagnosis and procedure codes are used to report diagnoses and hospital inpatient procedures. In the hospital outpatient, ambulatory surgery center, and physician office settings, Healthcare Common Procedure Coding System (HCPCS) codes are used to report procedures, items and services, including drugs, biologics, and supplies.

HCPCS consists of two levels of codes. The first level (Level I) consists of Current Procedural Terminology (CPT) codes that are primarily used to report services provided by physicians and other health care practitioners. CPT codes are established and maintained by the American Medical Association.

The second level (Level II) consists of alphanumeric HCPCS codes used to report items and services that are not billed using CPT codes, such as drugs, biologics, and supplies. Level II HCPCS codes are established and maintained by the Centers for Medicare & Medicaid Services (CMS).[1]

ICD-10-CM diagnosis codes

International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes describe the patient's medical condition.[2] Proper coding of diagnoses is essential and must be based on the information documented in the patient's medical record, without consideration of the adequacy of the reimbursement levels assigned by payers to specific codes. Coding conventions typically dictate that a patient's diagnosis (and treatment) be coded to the highest level of specificity possible. Below are ICD-10-CM diagnosis codes that may be applicable for patients to whom use of LUXTURNA® (voretigene neparvovec-rzyl) is indicated.

Per the US Full Prescribing Information, 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 physicians.[3]

ICD-10-CM diagnosis code[2]	Code descriptor
H35.50	Unspecified hereditary retinal dystrophy *Other indexing guidance for H35.50:* *Leber's congenital amaurosis* *Best's disease*
H35.52	Pigmentary retinal dystrophy *Retinitis pigmentosa*
H35.54	Dystrophies primarily involving the retinal pigment epithelium

Important Safety Information

Adverse Reactions (cont'd)

- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

References: 1. Centers for Medicare & Medicaid Services. HCPCS Level II Coding Procedures. Accessed January 6, 2022. https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/Downloads/2018-11-30-HCPCS-Level2-Coding-Procedure.pdf **2.** International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) (2022). **3.** LUXTURNA® US full Prescribing Information. Philadelphia, PA: Spark Therapeutics, Inc.; 2022.

Payer billing guidelines can facilitate claims processing and prompt payment (cont'd)

Procedure coding

The following CPT codes are possible codes to report the physician service of administering LUXTURNA®. Note that billing both a vitrectomy code and the unlisted procedure code on a single claim for one administration of LUXTURNA could be viewed by some payers as unbundling the subretinal injection from the overall procedure. CPT code 0810T is a new category III code effective July 1, 2023.[1] Please contact the payer directly to determine payer preference. However, when billing Medicare for the procedure of administering LUXTURNA, hospitals should use CPT code 0810T. CMS established HCPCS code C9770 effective January 1, 2021 but has since deleted the C code effective December 31, 2023 and will recognize only CPT code 0810T for the procedure effective January 1, 2024.[2]

CPT code[1]	Code descriptor
CPT 0810T	Subretinal injection of a pharmacologic agent, including vitrectomy and 1 or more retinotomies
CPT 67036	Vitrectomy, mechanical, pars plana approach
CPT 67299	Unlisted procedure, posterior segment

CPT=Common Procedural Terminology.

Modifiers should be included on the same line as the CPT code to identify the eye to which the LUXTURNA administration occurred.

Modifier	Descriptor
-RT	Right
-LT	Left

Coding for LUXTURNA

Effective January 1, 2019, a specific HCPCS J code is available to describe LUXTURNA. LUXTURNA is paid separately by Medicare when the administration procedure is reported using CPT code 0810T.[2] Payment for LUXTURNA by other payers may vary; please contact the payer for specifics.

Important Safety Information

Immunogenicity

Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Please see here for additional Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

References: 1. American Medical Association. CPT Category III Codes. Accessed July 1, 2023. https://www.amaassn.org/system/files/cpt-category3-codes-long-descriptors.pdf **2.** Centers for Medicare & Medicaid Services. Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems; Quality Reporting Programs; Payment for Intensive Outpatient Services in Hospital Outpatient Departments, Community Mental Health Centers, Rural Health Clinics, Federally Qualified Health Centers, and Opioid Treatment Programs; Hospital Price Transparency; Changes to Community Mental Health Centers Conditions of Participation, Changes to the Inpatient Prospective Payment System Medicare Code Editor; Rural Emergency Hospital Conditions of Participation Technical Correction. Accessed November 22, 2023. https://federalregister.gov/d/2023-24293

Payer billing guidelines can facilitate claims processing and prompt payment (cont'd)

Coding for LUXTURNA® (voretigene neparvovec-rzyl)

Effective January 1, 2019, a specific HCPCS J code is available to describe LUXTURNA. LUXTURNA is paid separately by Medicare when the administration procedure is reported using CPT code 0810T.[1] Payment for LUXTURNA by other payers may vary; please contact the payer for specifics.

As noted in the FDA-approved labeling, the recommended dose of LUXTURNA for each eye is 1.5×10^{11} (150 billion) vector genomes, administered by subretinal injection in a total volume of 0.3 mL.[2] With the J code descriptor of 1 billion vector genomes, the recommended dose for indication on the claim form would therefore be 150 units of J3398. Medicare has a Medically Unlikely edit for J3398 of 150 units, which means that providers may not bill more than 150 units of the code for a single patient on a single day.[3]

CMS calculates the payment rate for J3398 by dividing the ASP by 150 billing units, producing a reimbursement rate for 150 units that reflects the Average Sales Price (ASP) for the complete vial. Other payers may follow CMS calculations but please check with individual payers for specifics.

Important Safety Information

Pediatric Use

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 the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see here for additional Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

References: 1. Centers for Medicare & Medicaid Services. Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems; Quality Reporting Programs; Payment for Intensive Outpatient Services in Hospital Outpatient Departments, Community Mental Health Centers, Rural Health Clinics, Federally Qualified Health Centers, and Opioid Treatment Programs; Hospital Price Transparency; Changes to Community Mental Health Centers Conditions of Participation, Changes to the Inpatient Prospective Payment System Medicare Code Editor; Rural Emergency Hospital Conditions of Participation Technical Correction. Accessed November 22, 2023. https://federalregister.gov/d/ 2023-24293 **2.** LUXTURNA® [package insert]. Philadelphia, PA: Spark Therapeutics, Inc.; 2022. **3.** Facility Outpatient Hospital Services MUE Table. Effective 07-01-2023. Accessed 8/26/23. https://www.cms.govfiles/zip/medicare-ncci-facility-outpatient-hospital-services-mue-table-effective-07012023.zip

Payer billing guidelines can facilitate claims processing and prompt payment (cont'd)

J code

HCPCS code[1]	Code descriptor	Dosing units	Billable units per package
J3398	Injection, voretigene neparvovec-rzyl, 1 billion vector genomes	150 units	150 units

Modifiers for Claims With and Without Discarded Amounts from Single-Dose Containers

Effective July 1, 2023, Medicare requires providers and suppliers to report the JZ modifier (Zero drug amount discarded/not administered to any patient) on all claims for drugs that are separately payable under Medicare Part B when there are no discarded amounts from single-dose containers or single-use packages. Medicare continues to apply the policy, in effect since January 1, 2017, that requires providers and suppliers to report the JW modifier (Drug amount discarded/not administered to any patient) to identify any discarded amounts of drug.

When the full 150 billion vector genome dose of LUXTURNA® is administered, providers and suppliers would report 150 units of the HCPCS code with the JZ modifier, indicating that there are no discarded units of the drug.[2]

340B Coding and Billing

To comply with federal law and guidance from the Health Resources & Services Administration, 340B participating providers should complete all claims correctly and include appropriate code modifiers when billing Medicare or Medicaid for LUXTURNA that has been purchased at the 340B discounted price. 340B providers should also take special care to ensure Medicaid claims follow any state-specific guidelines.[3]

Important Safety Information

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

References: 1. Centers for Medicare & Medicaid Services. Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems; Quality Reporting Programs; Payment for Intensive Outpatient Services in Hospital Outpatient Departments, Community Mental Health Centers, Rural Health Clinics, Federally Qualified Health Centers, and Opioid Treatment Programs; Hospital Price Transparency; Changes to Community Mental Health Centers Conditions of Participation, Changes to the Inpatient Prospective Payment System Medicare Code Editor; Rural Emergency Hospital Conditions of Participation Technical Correction. Accessed November 22, 2023. https://federalregister.gov/d/2023-24293 **2.** Centers for Medicare & Medicaid Services. Medicare Hospital Outpatient Prospective Payment System and Ambulatory Surgical Center Payment System Final Rule. 87 FR 71988, 72082 – 72083. November 23, 2022. https://www.govinfo.gov/content/pkg/FR-2022-11-23/pdf/2022-23918.pdf. Accessed July 1, 2023. **3.** Health Resources & Services Administration. Duplicate Discount Prohibition. Accessed January 6, 2022. https://www.hrsa.gov/opa/program-requirements/medicaid-exclusion/index.html

Payer billing guidelines can facilitate claims processing and prompt payment (cont'd)

National Drug Codes (NDCs)

Medications approved by the FDA are assigned a 3-segment number known as the National Drug Code (NDC). Some payers, including Medicaid, require that products such as LUXTURNA® (voretigene neparvovec-rzyl) be billed with the product's NDC in addition to the HCPCS J code described on the previous page. Such payers may require a 10-digit or 11-digit NDC; exact requirements should be confirmed prior to submitting claims. LUXTURNA has been assigned the following NDCs:

NDC[1]	Package	Dosage form and strength
71394-415-01	10-digit for package (carton and pouch)	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 (5×10^{12} vector genomes/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2-mL vials.
71394-0415-01	11-digit for package (carton and pouch)	

Genetic Testing

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 physicians.[2] Codes that may be appropriate for describing genetic testing for identifying Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) due to biallelic *RPE65* gene mutations are described below. Note that a multi-panel test should only be performed when medical necessity for the panel is supported by documentation in the patient's medical record.

CPT Code[3]	Code Descriptor
Single Gene Test	
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
Multi-Panel Test	
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include analyses of at least 15 genes, including *ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A*

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

References: 1. US Food & Drug Administration. National Drug Code directory. Accessed January 6, 2022. https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory **2.** LUXTURNA® [package insert]. Philadelphia, PA: Spark Therapeutics, Inc.; 2022. **3.** American Medical Association. *CPT® 2022 Professional Edition*. 4th ed. American Medical Association Press; 2021.

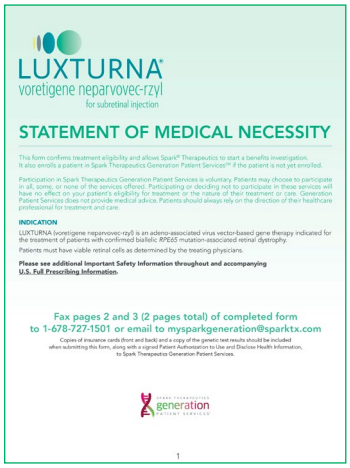
APPENDIX

Please see here for Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

Appendix

Reference the documents below as needed.

Statement of medical necessity form


LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

STATEMENT OF MEDICAL NECESSITY

This form confirms treatment eligibility and allows Spark® Therapeutics to start a benefits investigation. It also enrolls a patient in Spark Therapeutics Generation Patient Services℠ if the patient is not yet enrolled.

Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on your patient's eligibility for treatment or the nature of their treatment or care. Generation Patient Services does not provide medical advice. Patients should always rely on the direction of their healthcare professional for treatment and care.

INDICATION

LUXTURNA (voretigene neparvovec-rzyl) 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 physicians.

Please see additional Important Safety Information throughout and accompanying U.S. Full Prescribing Information.

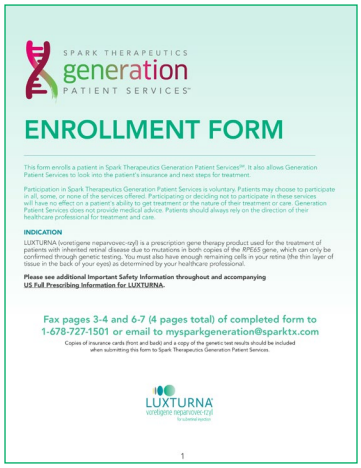
Fax pages 2 and 3 (2 pages total) of completed form to 1-678-727-1501 or email to mysparkgeneration@sparktx.com

Copies of insurance cards (front and back) and a copy of the genetic test results should be included when submitting this form, along with a signed Patient Authorization to Use and Disclose Health Information, to Spark Therapeutics Generation Patient Services.

generation

1

Spark Therapeutics Generation Patient Services® enrollment and patient authorization forms


SPARK THERAPEUTICS
generation
PATIENT SERVICES℠

ENROLLMENT FORM

This form enrolls a patient in Spark Therapeutics Generation Patient Services℠. It also allows Generation Patient Services to look into the patient's insurance and next steps for treatment.

Participation in Spark Therapeutics Generation Patient Services is voluntary. Patients may choose to participate in all, some, or none of the services offered. Participating or deciding not to participate in these services will have no effect on a patient's ability to get treatment or the nature of their treatment or care. Generation Patient Services does not provide medical advice. Patients should always rely on the direction of their healthcare professional for treatment and care.

INDICATION

LUXTURNA (voretigene neparvovec-rzyl) is a prescription gene therapy product used for the treatment of patients with inherited retinal disease due to mutations in both copies of the *RPE65* gene, which can only be confirmed through genetic testing. You must also have enough remaining cells in your retina (the thin layer of tissue in the back of your eyes) as determined by your healthcare professional.

Please see additional Important Safety Information throughout and accompanying US Full Prescribing Information for LUXTURNA.

Fax pages 3-4 and 6-7 (4 pages total) of completed form to 1-678-727-1501 or email to mysparkgeneration@sparktx.com

Copies of insurance cards (front and back) and a copy of the genetic test results should be included when submitting this form to Spark Therapeutics Generation Patient Services.

LUXTURNA®
voretigene neparvovec-rzyl

1

Important Safety Information

Warnings and Precautions (cont'd)

- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

Please see here for additional Important Safety Information for LUXTURNA.
Please see here for the US Full Prescribing Information for LUXTURNA.

P-RPE65-US-320025-9

Spark THERAPEUTICS

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUXTURNA safely and effectively. See full prescribing information for LUXTURNA.

LUXTURNA (voretigene neparvovec-rzyl) intraocular suspension for subretinal injection

Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------

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). (1)

----------DOSAGE AND ADMINISTRATION----------

For subretinal injection only.

- The recommended dose of LUXTURNA for each eye is 1.5 x 10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL. (2.1)
- Perform subretinal administration of LUXTURNA to each eye on separate days within a close interval, but no fewer than 6 days apart. (2.1)
- 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. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

LUXTURNA is a suspension for subretinal injection, supplied in a 0.5 mL extractable volume in a single-dose 2 mL vial for a single administration in one eye. The supplied concentration ($5x10^{12}$vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2-mL vials. (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Endophthalmitis: Use proper aseptic injection technique and monitor for signs and symptoms of infection. (5.1)
- Permanent decline in visual acuity: Monitor for visual disturbances. (5.2)
- Retinal abnormalities: Monitor for macular abnormalities, retinal tears or breaks and chorioretinal atrophy. Do not inject in the immediate vicinity of the fovea. (5.3)
- Increased intraocular pressure: Monitor and manage intraocular pressure elevations. (5.4)
- Expansion of intraocular air bubbles: Air travel and/or scuba diving is not recommended until any intraocular air bubbles have been absorbed. (5.5)
- Cataract: Subretinal injection of LUXTURNA may result in cataract formation or increase in the rate of cataract progression. (5.6)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥ 5%) in the clinical trials were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Spark Therapeutics, Inc. at 1-855-SPARKTX, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Pediatric use: Use in infants under 12 months of age is not recommended because of potential dilution or loss of LUXTURNA after administration due to the active retinal cell proliferation occurring in this age group. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

LUXTURNA (voretigene neparvovec-rzyl)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUXTURNA (voretigene neparvovec-rzyl) 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).

2 DOSAGE AND ADMINISTRATION

For subretinal injection only.

2.1 Dose

- The recommended dose of LUXTURNA for each eye is 1.5×10^{11} 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 the first eye), and followed by tapering the dose during the following 10 days. The same corticosteroid dosing regimen applies for the administration of LUXTURNA to the second eye. If the corticosteroid taper following LUXTURNA administration to the first eye is not complete three days prior to the planned LUXTURNA administration to the second eye, then the corticosteroid regimen for the second eye replaces the taper for the first eye.

2.2 Preparation

Prepare LUXTURNA within 4 hours of administration using sterile technique under aseptic conditions in a Class II vertical laminar flow biological safety cabinet (BSC). Below is the list of items required for dilution and administration syringe preparation:

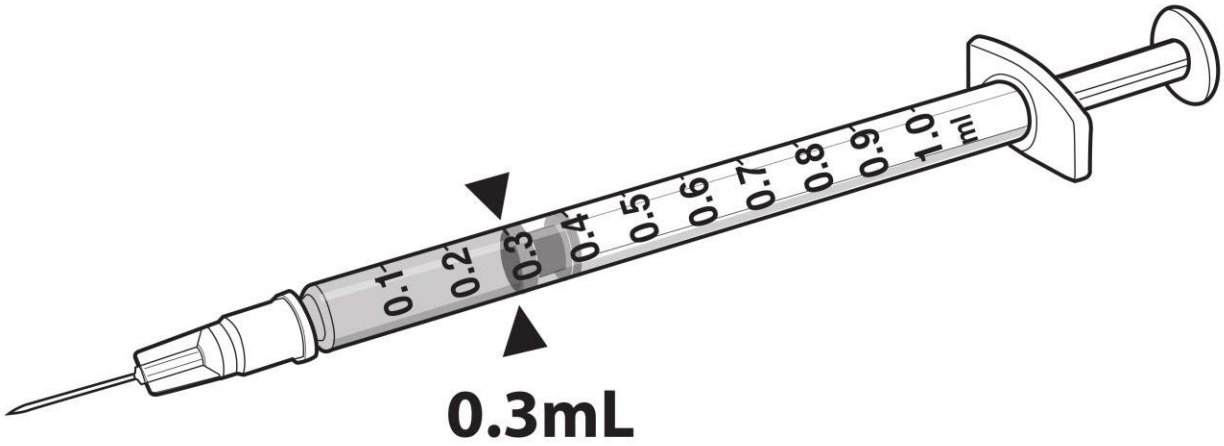
- One single-dose vial of LUXTURNA
- Two vials of Diluent
- One 3-mL sterile syringe
- One 20G 1-inch sterile needle
- Three 1-mL sterile syringes
- Three 27G ½-inch sterile needles
- Two sterile syringe caps
- One 10-mL sterile empty glass vial
- One sterile utility drape
- One sterile plastic bag
- Two sterile labels for administration syringes
- One sterile plain label
- One sterile skin marker

Dilution of LUXTURNA

1. Thaw one single-dose vial of LUXTURNA and two vials of Diluent at room temperature.
2. Mix the contents of the thawed Diluent vials by gently inverting them approximately 5 times.

3. Inspect the Diluent vials. If particulates, cloudiness, or discoloration are visible, do not use the vial(s); new vial(s) of Diluent should be used.
4. Obtain a 3-mL sterile syringe, a 20G 1-inch sterile needle, and a 10-mL sterile empty glass vial.
5. Using the 3-mL syringe with 20G 1-inch needle, transfer 2.7 mL of Diluent to the 10-mL glass vial. Dispose of the needle and syringe in an appropriate container.
6. Mix the contents of the thawed LUXTURNA single-dose vial by gently inverting approximately 5 times.
7. Inspect the LUXTURNA single-dose vial. If particulates, cloudiness, or discoloration are visible, do not use the vial; a new single-dose vial of LUXTURNA should be used.
8. Draw 0.3 mL of LUXTURNA into a 1-mL sterile syringe with a 27G ½-inch sterile needle. (Figure 1)

Figure 1. Syringe with 0.3 mL LUXTURNA



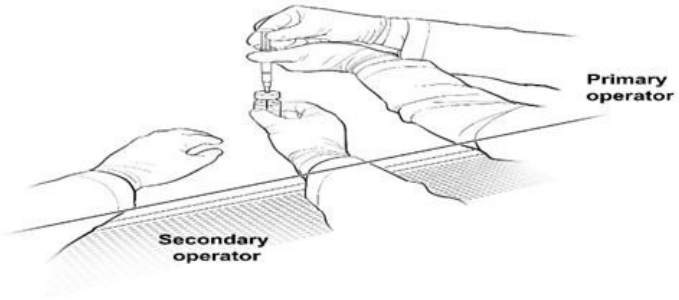
9. Transfer 0.3 mL of LUXTURNA to the glass vial containing 2.7 mL of Diluent from Step 5. Gently invert the 10-mL glass vial approximately 5 times to mix the contents.
10. Using the sterile plain label and sterile skin marker, label the 10-mL glass vial containing the diluted LUXTURNA as follows: “Diluted LUXTURNA”.
11. Remove all items from the BSC except the glass vial labeled ‘Diluted LUXTURNA’ and the sterile skin marker.
12. Re-sanitize the BSC prior to the next steps and place the glass vial and the sterile marker to the left side in the BSC.

Preparation of LUXTURNA for Injection

To keep the syringes sterile, two operators are required for transfer of the contents of the 10-mL glass vial labeled ‘Diluted LUXTURNA’ into each of two sterile 1-mL syringes.

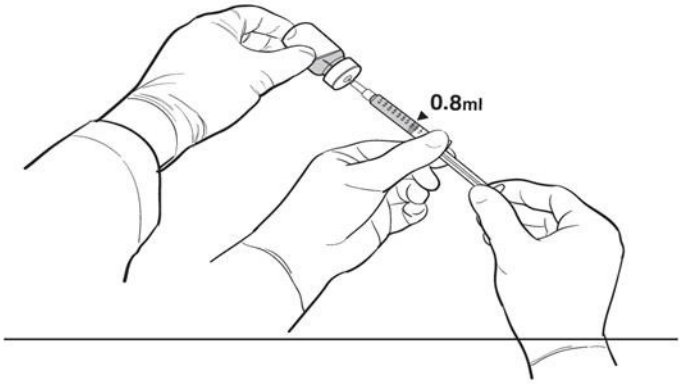
13. Place a sterile utility drape, a sterile plastic bag, and two sterile labels into the BSC.
14. Place the sterile drape near the Primary Operator on the right side of the sanitized BSC surface, away from the diluted LUXTURNA.
15. The Secondary Operator unwraps two 1-mL syringes, two 27G ½-inch needles, and two syringe caps in the BSC, ensuring that the Primary Operator touches only sterile surfaces while transferring the items onto the sterile drape.
16. The Secondary Operator changes to a new pair of sterile gloves and stands or sits to the left of the Primary Operator. The Secondary Operator holds the 10-mL glass vial containing the diluted LUXTURNA (Figure 2a).

Figure 2a. First Position of the Operators During Preparation of LUXTURNA Syringes



17. The Primary Operator withdraws 0.8 mL of the diluted LUXTURNA into a sterile 1-mL syringe using a 27G ½-inch sterile needle while the secondary operator holds the 10-mL glass vial. After the insertion of the needle, the Secondary Operator inverts the 10-mL glass vial enabling the Primary Operator to withdraw 0.8 mL without touching the 10-mL glass vial (Figure 2b).

Figure 2b. Second Position of the Operators During Preparation of LUXTURNA Syringes



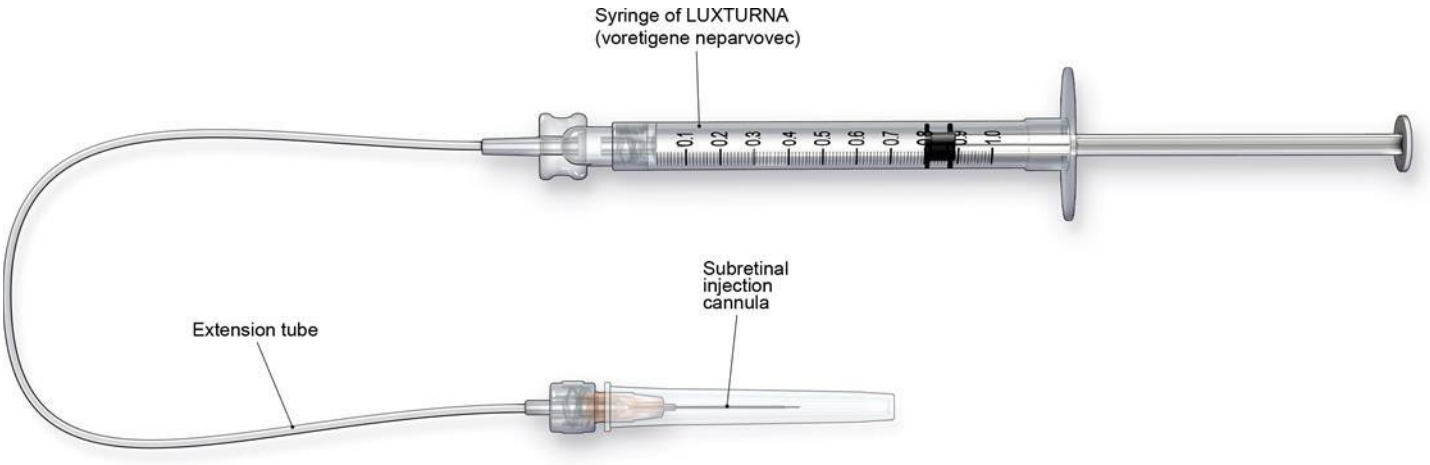
18. The Primary Operator removes the needle and affixes a sterile cap to the sterile syringe, disposes of the needle in an appropriate container, and attaches a sterile label to the administration syringe.
19. The Primary Operator repeats Steps 17 and 18 to prepare a total of two administration syringes. Label the first syringe “Diluted LUXTURNA” and label the second syringe “Back-up Diluted LUXTURNA” using the sterile skin marker. The second syringe will serve as a backup for the surgeon performing the subretinal administration procedure. Discard the back-up syringe after surgery if not used.
20. Inspect both syringes. If particulates, cloudiness, or discoloration are visible, do not use the syringe.
21. Place the syringes into the sterile plastic bag after visual inspection and seal the bag.
22. Place the sterile plastic bag with syringes containing diluted LUXTURNA into an appropriate secondary container (*e.g.,* hard plastic cooler) for delivery to the surgical suite at room temperature.

2.3 Administration

LUXTURNA should be administered in the surgical suite under controlled aseptic conditions by a surgeon experienced in performing intraocular surgery. In addition to the syringe containing the diluted LUXTURNA, the following items are required for administration:

- Subretinal injection cannula with a polyamide micro tip with an inner diameter of 41gauge.
- Extension tube made of polyvinyl chloride no longer than 6" (15.2 cm) in length and with an inner diameter no greater than 1.4mm**.**

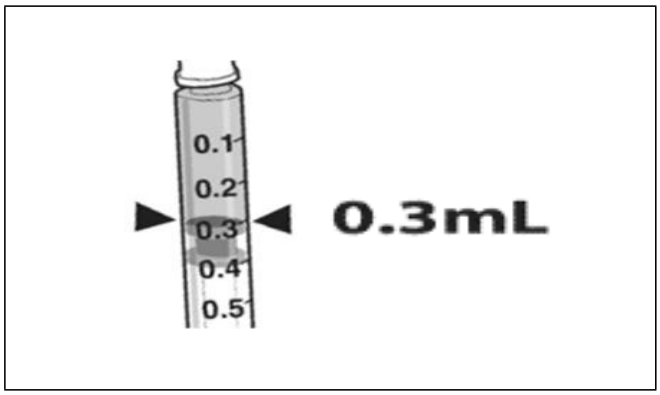
Figure 3. Injection Apparatus Assembly



Follow the steps below for subretinal injection:

1. After confirming the availability of LUXTURNA, dilate the eye and give adequate anesthesia to the patient.
2. Administer a topical broad spectrum microbiocide to the conjunctiva, cornea and eyelids prior to surgery.
3. Inspect LUXTURNA prior to administration. If particulates, cloudiness, or discoloration are visible, do not use the product.
4. Connect the syringe containing the diluted LUXTURNA to the extension tube and subretinal injection cannula. To avoid excess priming volume, the extension tube should not exceed 15.2 cm in length and 1.4 mm in inner diameter. Inject the product slowly through the extension tube and the subretinal injection cannula to eliminate any air bubbles.
5. Confirm the volume of product available in the syringe for injection, by aligning the plunger tip with the line that marks 0.3 mL. (Figure 4)

Figure 4. Volume of LUXTURNA for Injection



6. After completing a vitrectomy, identify the intended site of administration. The subretinal injection cannula can be introduced via pars plana. (Figure 5a)
7. Under direct visualization, place the tip of the subretinal injection cannula in contact with the retinal surface. The recommended site of injection is located along the superior vascular arcade, at least 2 mm distal to the center of the fovea (Figure 5b), avoiding direct contact with the retinal vasculature or with areas of pathologic features, such as dense atrophy or intraretinal pigment migration. Inject a small amount of the product slowly until an initial subretinal bleb is observed. Then inject the remaining volume slowly until the total 0.3 mL is delivered.

Figure 5a. Subretinal Injection Cannula Introduced via Pars Plana

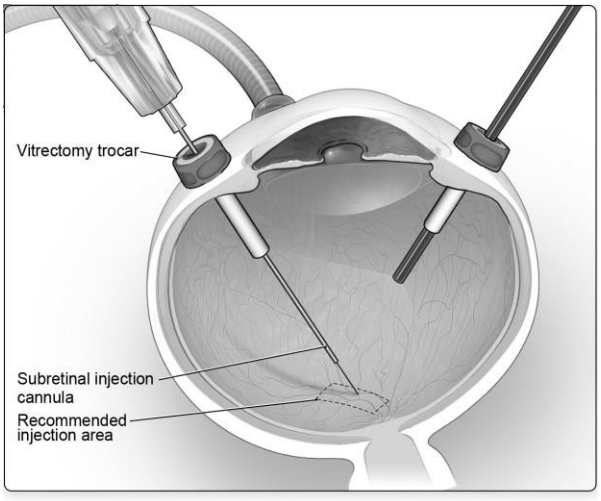
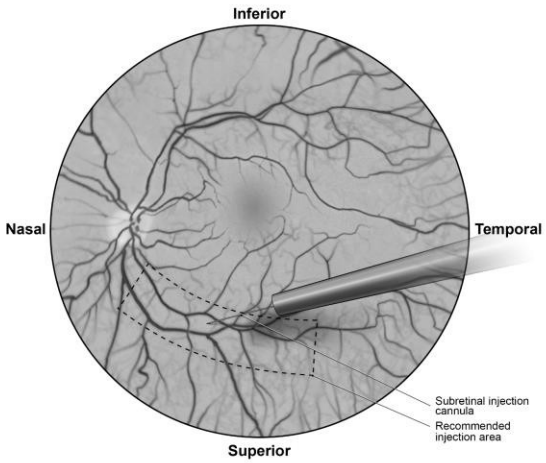


Figure 5b. Tip of the Subretinal Injection Cannula Placed Within the Recommended Site of Injection (Surgeon's Point of View)



8. After completing the injection, remove the subretinal injection cannula from the eye.
9. Following injection, discard all unused product. Dispose of the back-up syringe according to local biosafety guidelines applicable for handling and disposal of the product.
10. Perform a fluid-air exchange, carefully avoiding fluid drainage near the retinotomy created for the subretinal injection.
11. Initiate supine head positioning immediately in the post-operative period.
12. Upon discharge, advise patients to rest in a supine position as much as possible for 24 hours.

3 DOSAGE FORMS AND STRENGTHS

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 (5×10^{12} vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2 mL vials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis

Endophthalmitis may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA. Following the injection, monitor patients to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent Decline in Visual Acuity

Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal Abnormalities

Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, chorioretinal atrophy, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea *[see Dosage and Administration (2.3)]*.

Retinal abnormalities may occur during or following vitrectomy including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased Intraocular Pressure

Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of Intraocular Air Bubbles

Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract

Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5×10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety *[see Clinical Studies (14)]*. The average age of the 41 subjects was 17, years ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to voretigene neparvovec-rzyl, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection

Immunogenicity

At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinoid isomerohydrolase RPE65 [RPE65]).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of LUXTURNA. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye Disorders: chorioretinal atrophy (also reported as retinal degeneration, retinal depigmentation, and injection site atrophy).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the U.S. general population, the estimated

background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use

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.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 *[see Clinical Studies (14)]* that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use

The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

11 DESCRIPTION

LUXTURNA (voretigene neparvovec-rzyl) is a suspension of an adeno-associated virus vector-based gene therapy for subretinal injection. LUXTURNA is a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the human *RPE65* gene. LUXTURNA is derived from naturally occurring adeno-associated virus using recombinant DNA techniques.

Each single-dose vial of LUXTURNA contains 5×10^{12} vector genomes (vg) per mL, and the excipients 180 mM sodium chloride, 10 mM sodium phosphate, and 0.001% Poloxamer 188 (pH 7.3), in a 0.5-mL extractable volume. LUXTURNA requires a 1:10 dilution prior to administration. After dilution, each dose of LUXTURNA consists of 1.5×10^{11} vg in a deliverable volume of 0.3 mL.

The Diluent, supplied in 1.7 mL extractable volume per vial in two 2-mL vials, is composed of sterile water containing 180 mM sodium chloride, 10 mM sodium phosphate, and 0.001% Poloxamer 188 (pH 7.3).

LUXTURNA may also contain residual components of HEK293 cells including DNA and protein and trace quantities of fetal bovine serum.

The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LUXTURNA is designed to deliver a normal copy of the gene encoding the human retinoid isomerohydrolase RPE65 (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 (RPE) cells and converts all-*trans*-retinol to 11-*cis*-retinol, which subsequently forms the chromophore, 11-*cis*-retinal, during the visual (retinoid) 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 retinoid isomerohydrolase RPE65 activity, blocking the visual cycle and resulting in impairment of vision.

12.2 Pharmacodynamics

Injection of LUXTURNA into the subretinal space results in transduction of some retinal pigment epithelial cells with a cDNA encoding normal human RPE65 protein, thus providing the potential to restore the visual cycle.

12.3 Pharmacokinetics

Biodistribution (within the body) and Vector Shedding (excretion/secretion)

LUXTURNA vector DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction (qPCR) assay.

Nonclinical data

Biodistribution of LUXTURNA was evaluated at three months following subretinal administration in non-human primates. The highest levels of vector DNA sequences were detected in intraocular fluids (anterior chamber fluid and vitreous) 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. Vector DNA sequences were not detected in the gonads.

Clinical data

LUXTURNA vector shedding and biodistribution were investigated in a study measuring LUXTURNA DNA in tears from both eyes, and from serum, and whole blood of subjects in Study 2. In summary, LUXTURNA vector was shed transiently and at low levels in tears from the injected eye in 45% of the subjects in Study 2, and occasionally (7%) from the uninjected eye until Day 3 post-injection.

In 29 subjects who received bilateral administrations, LUXTURNA vector DNA was present in tear samples of 13 subjects (45%). Peak levels of vector DNA were detected in the tear samples on Day 1 post-injection, after which no vector DNA was detected in a majority of the subjects (8 of 13). Three subjects (10%) had vector DNA in tear samples until Day 3 post-injection, and two subjects (7%) had vector DNA in tear samples for around two weeks post-injection. In another two subjects (7%), vector DNA was detected in tear samples from the uninjected (or previously injected) eye until Day 3 post-injection. Vector DNA was detected in serum in 3/29 (10%) subjects, including two with vector DNA in tear samples up to Day 3 following each injection.

Specific Populations

No pharmacokinetic studies with LUXTURNA have been conducted.

Drug Interaction Studies

No interaction studies have been performed with LUXTURNA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted to evaluate the effects of LUXTURNA on carcinogenesis, mutagenesis, and impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

Bilateral, simultaneous subretinal administration of LUXTURNA was well tolerated at dose levels up to 8.25 x 10^{10} vg per eye in dogs with a naturally occurring RPE-65 mutation and 7.5 x 10^{11} vg (5 times higher than the recommended human dose level) per eye in non-human primates (NHPs) with normal-sighted eyes. In both animal models, bilateral, sequential subretinal administrations, where the contralateral eye was injected following the first eye, were well tolerated at the recommended human dose level of 1.5 x 10^{11} vg per eye. In addition, dogs with the RPE-65 mutation displayed improved visual behavior and pupillary responses. Ocular histopathology showed only mild changes, which were mostly related to healing from the surgical administration procedure. Other findings observed following subretinal injection of LUXTURNA in dogs and NHPs included occasional and isolated inflammatory cells in the retina, with no apparent retinal degeneration. Dogs not previously exposed to AAV2 vectors developed antibodies to the AAV2 capsid following a single administration of LUXTURNA, whereas NHPs did not.

14 CLINICAL STUDIES

The efficacy of LUXTURNA in pediatric and adult patients with biallelic *RPE65* mutation-associated retinal dystrophy was evaluated in an open-label, two-center, randomized trial (Study 2). Of the 31 enrolled subjects, 21 subjects were randomized to receive subretinal injection of LUXTURNA. One subject discontinued from the study prior to treatment. Ten subjects were randomized to the control (non-intervention) group. One subject in the control group withdrew consent and was discontinued from the study. The nine subjects who were randomized to the control group were crossed over to receive subretinal injection of LUXTURNA after one year of observation. The average age of the 31 randomized subjects was 15 years (range 4 to 44 years), including 64% pediatric subjects (n=20, age from 4 to 17 years) and 36% adults (n=11). The 31 randomized subjects included 13 males and 18 females. Sixty-eight percent (68%) of the subjects were White, 16% were Asian, 10% were American Indian or Alaska Native, and 6% were Black or African-American. Bilateral subretinal injections of LUXTURNA were administered sequentially in two separate surgical procedures with an interval of 6 to 18 days.

The efficacy of LUXTURNA 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. The MLMT was assessed using both eyes and each eye separately at one or more of seven levels of illumination, ranging from 400 lux (corresponding to a brightly lit office) to 1 lux (corresponding to a moonless summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a subject was able to pass the MLMT at a lower light level. A score of -1 was assigned to subjects who could not pass MLMT at a light level of 400 lux. The MLMT of each subject was videotaped and assessed by independent graders. The MLMT score was determined by the lowest light level at which the subject was able to pass the MLMT. The MLMT score change was defined as the difference between the score at Baseline and the score at Year 1. A positive MLMT score change from Baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level.

Additional clinical outcomes were also evaluated, including full-field light sensitivity threshold (FST) testing, visual acuity, and visual fields.

Table 2 summarizes the median MLMT score change from Baseline to Year 1 in the LUXTURNA treatment group as compared to the control group. A median MLMT score change of 2 was observed in the LUXTURNA treatment group, while a median MLMT score change of 0 was observed in the control group, when using both eyes or the first-treated eye. An MLMT score change of two or greater is considered a clinically meaningful benefit in functional vision.

Table 2. Efficacy Results of Study 2 at Year 1, Compared to Baseline

Efficacy Outcomes	LUXTURNA n=21	Control n=10	Difference (LUXTURNA minus Control)	p-value
MLMT score change for bilateral eyes, median (min, max)	2 (0, 4)	0 (-1, 2)	2	0.001
MLMT score change for first-treated eye, median (min, max)	2 (0, 4)	0 (-1, 1)	2	0.003

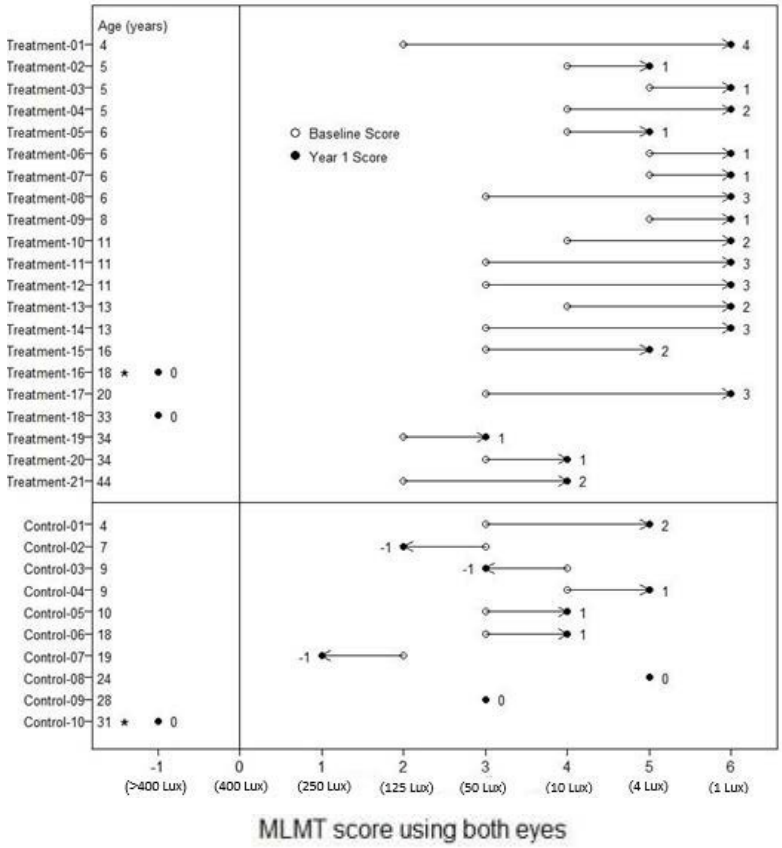
Table 3 shows the number and percentage of subjects with different magnitudes of MLMT score change using both eyes at Year 1. Eleven of the 21 (52%) subjects in the LUXTURNA treatment group had an MLMT score change of two or greater, while one of the ten (10%) subjects in the control group had an MLMT score change of two.

Table 3. Magnitude of MLMT Score Change Using Both Eyes at Year 1 (Study 2)

Score Change	LUXTURNA n=21	Control n=10
-1	0	3 (30%)
0	2 (10%)	3 (30%)
1	8 (38%)	3 (30%)
2	5 (24%)	1 (10%)
3	5 (24%)	0
4	1 (4%)	0

Figure 6 shows MLMT performance of individual subjects using both eyes at Baseline and at Year 1.

Figure 6. MLMT Score Using Both Eyes at Baseline and Year 1 for Individual Subjects (Study 2)

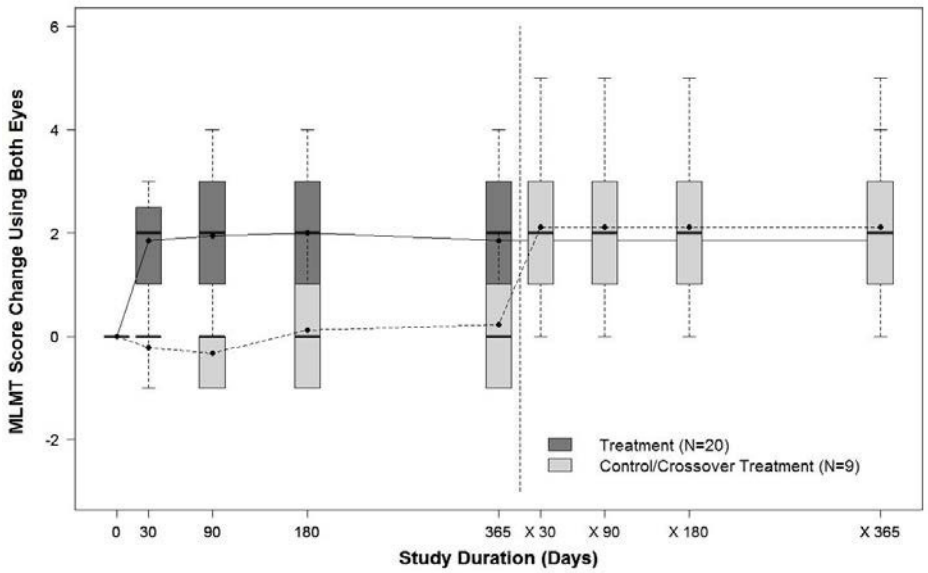


Note for Figure 6: *subjects who were withdrawn or discontinued. The open circles are the baseline scores. The closed circles are the Year 1 scores. The numbers next to the solid circle represent score change at Year 1. The horizontal lines with arrows represent the magnitude of the score change and its direction. Arrows pointing towards the right represent improvement. The top section shows the results of the 21 subjects in the treatment group. The bottom section shows the results of the 10 subjects in the control group. Subjects in each group are chronologically organized by age, with the youngest subject at the top and the oldest subject at the bottom.

Analysis of white light FST testing showed statistically significant improvement from Baseline to Year 1 in the LUXTURNA treatment group compared to the control group. The change in visual acuity from Baseline to Year 1 was not significantly different between the LUXTURNA and control groups.

Figure 7 shows the effect of LUXTURNA over the two-year period in the LUXTURNA treatment group, as well as the effect in the control group after crossing over to receive subretinal injection of LUXTURNA. A median MLMT score change of two was observed for the LUXTURNA treatment group at Day 30, and this effect was sustained over the remaining follow-up visits throughout the two-year period. For the control group, a median MLMT score change of 0 was observed at all four follow up visits during the first year. However, after crossing-over to receive subretinal injection of LUXTURNA, the subjects in the control group showed a similar response to LUXTURNA as compared to the subjects in the LUXTURNA treatment group.

Figure 7. MLMT Time-Course over Two Years: Using Both Eyes (Study 2)



Note for Figure 7: Each box represents the middle 50% of distribution of MLMT score change. Vertical dotted lines represent additional 25% above and below the box. The horizontal bar within each box represents the median. The dot within each box represents the mean. The solid line connects the mean MLMT score changes over visits for the treatment group, including five visits during the first year and one visit at Year 2 (marked as x365). The dotted line connects the mean MLMT score change over visits for the control group, including five visits during the first year without receiving LUXTURNA, and four visits within the second year (marked as x30, x90, x180, and x365) after cross-over at Year 1 to receive LUXTURNA.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each carton of LUXTURNA (NDC 71394 – 415-01) contains one single-dose vial of the LUXTURNA (NDC 71394 – 065-01, 0.5 mL extractable volume) and two vials of Diluent (NDC 71394 – 716-01, 1.7 mL extractable volume in each vial). LUXTURNA contains 5 x 10^{12} vector genomes (vg) per mL and requires a 1:10 dilution prior to administration.

Store LUXTURNA and Diluent frozen at ≤ -65 °C.

Following thaw of the vials, store at room temperature. Store diluted LUXTURNA at room temperature [See Dosage and Administration 2.2].

LUXTURNA is an adeno-associated virus vector-based gene therapy. Follow universal biohazard precautions for handling.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or their caregivers of the following risks:

- Endophthalmitis and other eye infections

  Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

- Permanent decline in visual acuity

  Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

- Retinal abnormalities

Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina, loss of retinal cells and the choroid (layer of blood vessels that line the back of the eye), or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

- Increased intraocular pressure

  Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow-up with their healthcare provider to detect and treat any increase in intraocular pressure.

- Expansion of intraocular air bubbles

  Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

- Cataract

  Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

- Shedding of LUXTURNA

  Transient and low level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

Manufactured by:
Spark Therapeutics, Inc.
3737 Market Street
Philadelphia, PA 19104

US License #2056