Package leaflet: Information for the patient

Luxturna 5 × 10^{12} vector genomes/mL concentrate and solvent for solution for injection
voretigene neparvovec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Luxturna is and what it is used for

Luxturna is a gene therapy product that contains the active substance voretigene neparvovec.

Luxturna is used for the treatment of adults and children with vision loss due to inherited retinal dystrophy caused by mutations in the *RPE65* gene. These mutations prevent the body from producing a protein needed for vision and so lead to loss of sight and eventual blindness.

The active substance in Luxturna, voretigene neparvovec, is a modified virus that contains a working copy of the *RPE65* gene. After injection it delivers this gene into the cells of the retina, the layer at the back of the eye that detects light. This enables the retina to produce the proteins needed for vision. The virus used to deliver the gene does not cause disease in humans.

Luxturna will be given to you only if genetic testing shows that your vision loss is caused by mutations in the *RPE65* gene.

2. What you need to know before you are given Luxturna

You will not be given Luxturna
- if you are allergic to voretigene neparvovec or any of the other ingredients of this medicine (listed in section 6)
- if you have an eye infection
- if you have eye inflammation

If any of the above applies to you, or if you are unsure of any of the above, please talk to your doctor before you receive Luxturna.

Warnings and precautions
Before receiving treatment with Luxturna:
- Tell your doctor if you have signs of an eye infection or eye inflammation, for example if you

have eye redness, sensitivity to light, eye swelling or eye pain.
- Tell your doctor if you have an active infection of any sort. Your doctor may delay your treatment until your infection is gone because this medicine may make it more difficult for you to fight an infection. See also section 3.

After receiving Luxturna:
- Get immediate care from your doctor if your eye or eyes become red, painful, sensitive to light, you see flashes or floaters in your vision, or if you notice any worsening or blurred vision.
- You should avoid air travel or other travel to high elevations until advised by your doctor. During treatment with this medicine, the doctor inserts an air bubble in the eye, which is slowly absorbed by your body. Until the bubble is fully absorbed, air travel or other travel to high elevations may make the bubble expand and lead to eye damage, including vision loss. Please talk to your doctor before travelling.
- You should avoid swimming because of an increased risk of infection in the eye. Please talk to your doctor before going to swim after receiving treatment with Luxturna.
- You should avoid strenuous physical activity because of an increased risk of injury to the eye. Please talk to your doctor before beginning to engage in strenuous physical activity after receiving Luxturna.
- You may have temporary visual disturbances, such as light sensitivity, and blurred vision. Tell your doctor about any visual disturbances that you experience. Your doctor may be able to help reduce any discomfort caused by these temporary disturbances.
- The active substance in Luxturna may temporarily be excreted through your tears. You and your caregiver should place any used dressings and waste material with tears and nasal secretions in sealed bags before disposing of them. You should follow these precautions for 14 days.
- You might not be able to donate blood, organs, tissues and cells for transplantation after you have been treated with Luxturna.

Children and adolescents
Luxturna has not been studied in children below 4 years of age. Data are limited.

Other medicines and Luxturna
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you might be pregnant, or are planning to have a baby, ask your doctor or nurse for advice before being treated with Luxturna.

The effects of this medicine on pregnancy and the unborn child are not known. As a precaution, you should not receive Luxturna while you are pregnant.

Luxturna has not been studied in breast-feeding women. It is not known whether it passes into breast milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding or to not receive Luxturna, taking into account the benefit of breast-feeding for your baby and the benefit of Luxturna for you.

Driving and using machines
You may have temporary visual disturbances after receiving Luxturna. Do not drive or use heavy machines until your vision has recovered. Talk to your doctor before resuming these activities.

Luxturna contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How Luxturna is given to you

Luxturna will be given to you in an operating room by surgeons experienced in performing eye

surgery.

Luxturna is given under anaesthesia. Your doctor will talk to you about the anaesthesia and how it will be given to you.

Your doctor will carry out eye surgery to remove the clear gel inside the eye, and then inject Luxturna directly under your retina, the thin light-sensing layer at the back of that eye. This will be repeated on your other eye at least 6 days afterwards. You will need to stay for post-operative observation for a few hours after each procedure to monitor your recovery and watch for any side effects from the surgery or the anaesthesia.

Before Luxturna treatment is started your doctor may ask you to take a medicine that will suppress your immune system (the body's natural defences) so that it will not try to fight the Luxturna when it is given. It is important that you take this medicine according to the instructions given. Do not stop taking the medicine without first talking to your doctor.

If you are given more Luxturna than you should be
As this medicine is given to you by a doctor, it is unlikely that you will be given too much. If it does occur, your doctor will treat the symptoms as necessary. Tell your doctor or nurse if you have any visual problems.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may happen with Luxturna:

Common (may affect up to 1 in 10 people)
- Deposits under the retina

The following side effects may happen with the injection procedure:

Very common (may affect more than 1 in 10 people)
- Redness of the eye
- Cataract (clouding of the lens)
- Increased pressure in the eye

Common (may affect up to 1 in 10 people)
- Break in the retina
- Eye pain
- Eye swelling
- Detachment of the retina
- Bleeding in the back of the eye
- Pain or increased discomfort in the eye
- Blurring of central vision due to hole in the centre of the retina
- Thinning of the surface of the eye (dellen)
- Eye irritation
- Eye inflammation
- Foreign body sensation in the eye
- Eye discomfort
- Abnormalities in the back of the eye
- Nausea (feeling sick), vomiting, abdominal (belly) pain, lip pain
- Change of the electrical activity of the heart

- Headache, dizziness
- Rash, facial swelling
- Anxiety
- Problems associated with the placement of a breathing tube in the windpipe
- Breakdown of the surgical wound

Not known (frequency cannot be estimated from the available data)
- Clouding in the gel-like substance inside the eye (vitreous opacities)
- Atrophy of the (chorio)retina

Damage to the tissues of the eye may be accompanied by bleeding and swelling and an increased risk of infection. There is reduced vision in the days after surgery that usually improves; tell your doctor if vision does not return.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see below details). By reporting side effects, you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

5. How Luxturna is stored

Luxturna will be stored by the healthcare professionals at your healthcare facility.
Concentrate and solvent must be stored and transported frozen at ≤-65 ºC. Once thawed, the medicine should not be re-frozen and should be left at room temperature (below 25 °C).
Do not use this medicine after the expiry date which is stated on the label and carton after EXP.

6. Contents of the pack and other information

What Luxturna contains
- The active substance is voretigene neparvovec. Each mL of concentrate contains 5×10^{12} vector genomes (vg). The concentrate (0.5 mL extractable volume in a single-dose 2 mL vial) requires a 1:10 dilution prior to administration.
- Each dose of diluted solution contains 1.5×10^{11} vector genomes of voretigene neparvovec in a deliverable volume of 0.3 mL.
- The other ingredients of the concentrate are sodium chloride (see "Luxturna contains sodium" in section 2 of this leaflet), sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate dihydrate (for pH adjustment), poloxamer 188 and water for injections.
- The solvent contains sodium chloride (see end of section 2), sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate dihydrate (for pH adjustment), poloxamer 188 and water for injections.

This medicine contains genetically modified organisms.

What Luxturna looks like and contents of the pack
Luxturna is a clear, colourless concentrate for solution for subretinal injection, supplied in a clear plastic vial. The solvent is a clear, colourless liquid supplied in a clear plastic vial.

Each foil pouch includes a carton containing 1 vial of 0.5 mL concentrate and 2 vials of solvent (each containing 1.7 mL).

Marketing Authorisation Holder
Novartis Pharmaceuticals UK Limited
2nd Floor, The WestWorks Building
White City Place, 195 Wood Lane
London, W12 7FQ
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

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Other sources of information
This leaflet is available as an audio file and in a large print from the web site:
http://www.voretigeneneparvovec.support

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified organisms. Personal protective equipment (to include laboratory coat, safety glasses and gloves) should be worn while handling or administering voretigene neparvovec.

Intraocular pressure should be monitored prior to and following administration of the medicinal product and managed appropriately.

Following the administration, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Preparation prior to administration

Each pack contains 1 vial of concentrate and 2 vials of solvent for single use only.

Luxturna should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the single-dose vial must not be used.

Preparation of Luxturna should be performed within 4 hours of beginning the administration procedure, in accordance with the following recommended procedure performed under aseptic

conditions.

Thaw one single-dose vial of concentrate and two vials of solvent at room temperature. Once all 3 vials (1 vial of concentrate and 2 vials of diluent) are thawed, dilution should be initiated. Gently invert the vials five times to mix the contents.

Inspect for any visual particulates or any anomalies. Any anomalies or appearance of visual particulates should be reported to the Marketing Authorisation Holder and product should not be used.

Transfer 2.7 mL of solvent taken from the two thawed vials and dispense into a sterile 10 mL empty glass vial using a 3 mL syringe.

For dilution, draw 0.3 mL of thawed concentrate into a 1 mL syringe and add it to the 10 mL sterile vial containing the solvent. Gently invert the vial at least five times for proper mixing. Inspect for any visual particulates. The diluted solution should be clear to slightly opalescent. Label the 10 mL glass vial containing the diluted concentrate as follows: 'Diluted Luxturna'.

Do not prepare syringes if the vial shows any damage or if any visual particulates are observed. Prepare the syringes for injection by drawing 0.8 mL of the diluted solution into a sterile 1 mL syringe. Repeat the same procedure to prepare a backup syringe. The product-filled syringes should then be transferred in a designated transport container to the surgical suite.

Measures to take in case of accidental exposure

Accidental exposure must be avoided. Local biosafety guidelines for preparation, administration and handling of voretigene neparvovec should be followed.

- Personal protective equipment (to include laboratory coat, safety glasses and gloves) should be worn while handling or administering voretigene neparvovec.
- Accidental exposure to voretigene neparvovec, including contact with skin, eyes and mucous membranes, is to be avoided. Any exposed wounds should be covered before handling.
- All spills of voretigene neparvovec must be treated with a virucidal agent such as 1% sodium hypochlorite and blot using absorbent materials.
- All materials that may have come in contact with voretigene neparvovec (e.g. vial, syringe, needle, cotton gauze, gloves, masks or dressings) must be disposed of in accordance with local biosafety guidelines.

Accidental exposure

- In the event of an accidental occupational exposure (e.g. through a splash to the eyes or mucous membranes), flush with clean water for at least 5 minutes.
- In the event of exposure to broken skin or needlestick injury, clean the affected area thoroughly with soap and water and/or a disinfectant.

Precautions to be taken for the disposal of the medicinal product

This medicinal product contains genetically modified organisms. Unused medicinal product or waste material must be disposed of in compliance with the local guidance for pharmaceutical waste.

Posology

Treatment should be initiated and administered by a retinal surgeon experienced in performing macular surgery.

Patients will receive a single dose of 1.5×10^{11} vector genomes voretigene neparvovec in each eye. Each dose will be delivered into the subretinal space in a total volume of 0.3 mL. The individual administration procedure to each eye is performed on separate days within a close interval, but no fewer than 6 days apart.

Immunomodulatory regimen
Prior to initiation of the immunomodulatory regimen and prior to administration of voretigene neparvovec, the patient must be checked for symptoms of active infectious disease of any nature, and in case of such infection the start of treatment must be postponed until after the patient has recovered.

Starting 3 days prior to the administration of voretigene neparvovec to the first eye, it is recommended that an immunomodulatory regimen is initiated following the schedule below (Table 1). Initiation of the immunomodulatory regimen for the second eye should follow the same schedule and supersede completion of the immunomodulatory regimen of the first eye.

Table 1 Pre- and post-operative immunomodulatory regimen for each eye

Pre-operative	3 days prior to Luxturna administration	Prednisone (or equivalent) 1 mg/kg/day (maximum of 40 mg/day)
Post-operative	4 days (including the day of administration)	Prednisone (or equivalent) 1 mg/kg/day (maximum of 40 mg/day)
	Followed by 5 days	Prednisone (or equivalent) 0.5 mg/kg/day (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day	Prednisone (or equivalent) 0.5 mg/kg every other day (maximum of 20 mg/day)

Special populations
Elderly
The safety and efficacy of voretigene neparvovec in patients ≥65 years old have not been established. Data are limited. However, no adjustment in dose is necessary for elderly patients.

Hepatic and renal impairment
The safety and efficacy of voretigene neparvovec have not been established in patients with hepatic or renal impairment. No dose adjustment is required in these patients (see section 5.2).

Paediatric population
The safety and efficacy of voretigene neparvovec in children aged up to 4 years have not been established. Data are limited. No adjustment in dose is necessary for paediatric patients.

Method of administration

Subretinal use.

Luxturna is a sterile concentrate solution for subretinal injection that requires thawing and dilution prior to administration.

This medicinal product must not be administered by intravitreal injection.

Luxturna is a single-use vial for a single administration in one eye only. The product is administered as a subretinal injection after vitrectomy in each eye. It should not be administered in the immediate vicinity of the fovea to maintain foveal integrity.

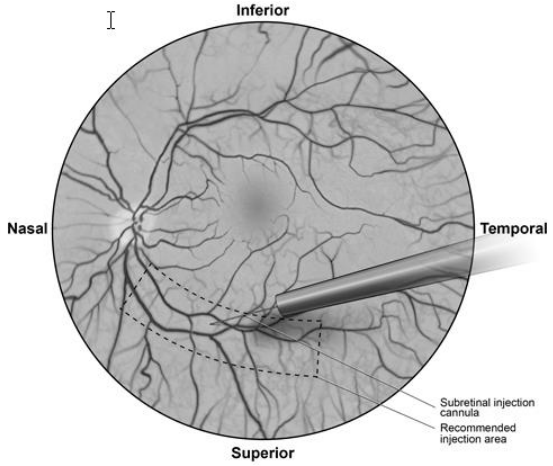
The administration of voretigene neparvovec should be carried out in the surgical suite under controlled aseptic conditions. Adequate anaesthesia should be given to the patient prior to the procedure. The pupil of the eye to be injected must be dilated and a broad-spectrum microbiocide should be topically administered prior to the surgery according to standard medical practice.

Administration

Follow the steps below to administer voretigene neparvovec to patients:

- Diluted Luxturna should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the medicinal product must not be used.
- Connect the syringe containing the diluted product to the extension tube and subretinal injection cannula. The product is slowly injected through the extension tube and subretinal injection cannula to eliminate any air bubbles in the system.
- The volume of product available for injection is confirmed in the syringe, by aligning the plunger tip with the line that marks 0.3 mL.
- After vitrectomy is completed, Luxturna is administered by subretinal injection using a subretinal injection cannula introduced via pars plana.
- Under direct visualisation, the tip of the subretinal injection cannula is placed in contact with the retinal surface. The recommended site of injection should be located along the superior vascular arcade, at least 2 mm distal to the centre of the fovea. A small amount of the product is slowly injected until an initial subretinal bleb is observed, and then the remaining volume is slowly injected until the total 0.3 mL is delivered (Figure 1).

Figure 1 Tip of the subretinal injection cannula placed within recommended site of injection (surgeon's view)



- At the completion of the injection, the subretinal injection cannula is removed from the eye.
- After injection, any unused product must be discarded. The back-up syringe may not be retained.
- Fluid-air exchange is performed, carefully avoiding fluid drainage near the retinotomy created for the subretinal injection.
- Supine head positioning is initiated immediately in the post-operative period and, upon discharge should be maintained by the patient for 24 hours.