▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Voretigene neparvovec is a gene transfer vector that employs an adeno-associated viral vector serotype 2 (AAV2) capsid as a delivery vehicle for the human retinal pigment epithelium 65 kDa protein (hRPE65) cDNA to the retina. Voretigene neparvovec is derived from wild-type AAV2 using recombinant DNA techniques.

2.2 Qualitative and quantitative composition

Each mL of concentrate contains 5×10^{12} vector genomes (vg).

Each vial of Luxturna contains 0.5 extractable mL of concentrate (corresponding to 2.5×10^{12} vector genomes) which requires a 1:10 dilution prior to administration, see section 6.6.

After dilution of 0.3 mL of concentrate with 2.7 mL of solvent, each mL contains 5×10^{11} vector genomes. Each dose of 0.3 mL Luxturna contains $1.5 \text{ x } 10^{11}$ vector genomes.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate and solvent for solution for injection.

Following thaw from their frozen state, both the concentrate and the solvent are clear, colourless liquids with a pH of 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells.

4.2 Posology and method of administration

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

<u>Posology</u>

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 (see section 6.6).

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 (see section 4.4).

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 microbicide

should be topically administered prior to the surgery according to standard medical practice.

For instructions for preparation, accidental exposure to and disposal of Luxturna, see section 6.6.

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 (Figure 1A).
- 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 (Figure 1B). 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 1A Subretinal injection cannula introduced via pars plana

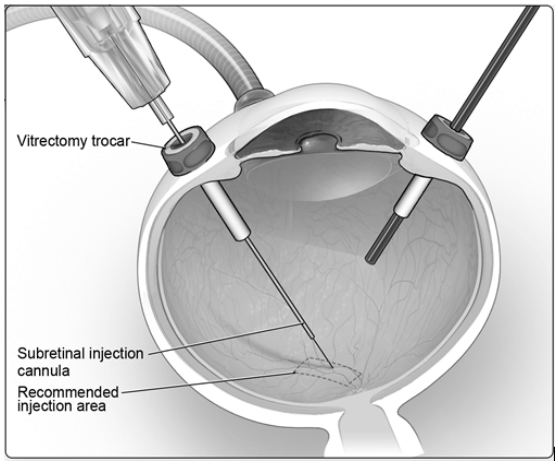
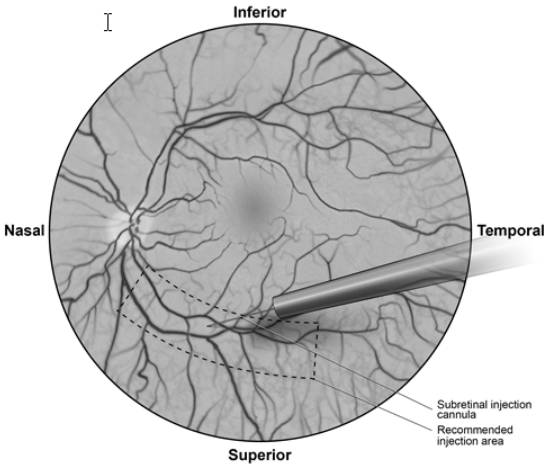


Figure 1B Tip of the subretinal injection cannula placed within the recommended site of injection (surgeon's view)



- 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.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
Ocular or periocular infection.
Active intraocular inflammation.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Subretinal injection-related reactions

Proper aseptic techniques should always be used for the preparation and administration of Luxturna.

The following adverse reactions have been observed with the administration procedure:
- Eye inflammation (including endophthalmitis), retinal tear and retinal detachment. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- Retinal disorder (foveal thinning, loss of foveal function), macular hole, maculopathy (epiretinal membrane, macular pucker) and eye disorder (foveal dehiscence).
- Increase in intraocular pressure. Intraocular pressure should be monitored prior to and following administration of the medicinal product and managed appropriately. Patients should be instructed to avoid air travel or other travel to high elevations until the air bubble formed as a result of administration of Luxturna has completely dissipated from the eye. A time period of up to one week or more following injection may be required before dissipation of the air bubble; this should be verified on ophthalmic examination. A rapid increase in altitude while the air bubble is still present can cause a rise in eye pressure and irreversible vision loss.

Temporary visual disturbances, such as blurred vision and photophobia (see section 4.8), may occur during the weeks that follow the treatment. Patients should be instructed to contact their healthcare professional if visual disturbances persist. Patients should avoid swimming because of an increased risk of infection in the eye. Patients should avoid strenuous physical activity because of an increased risk of injury to the eye. Patients may resume swimming and strenuous activity, after a minimum of one to two weeks, on the advice of their healthcare professional.

Shedding

Transient and low-level vector shedding may occur in patient tears (see section 5.2).
Patients/caregivers should be advised to handle waste material generated from dressings, tears and nasal secretion appropriately, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for 14 days after administration of voretigene neparvovec. It is recommended that patients/caregivers wear gloves for dressing changes and waste disposal, especially in case of underlying pregnancy, breast-feeding and immunodeficiency of caregivers.

Blood, organ, tissue and cell donation

Patients treated with Luxturna should not donate blood, organs, tissues and cells for transplantation.

Immunogenicity

To reduce the potential for immunogenicity patients should receive systemic corticosteroids before and after the subretinal injection of voretigene neparvovec to each eye (see section 4.2). The corticosteroids may decrease the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known clinically significant interactions. No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Based on non-clinical studies and clinical data from trials of AAV2 vectors, and considering the subretinal route of administration of Luxturna, inadvertent germ-line transmission with AAV vectors is highly unlikely.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of voretigene neparvovec in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Luxturna during pregnancy.

Breast-feeding

Luxturna has not been studied in breast-feeding women. It is unknown whether voretigene neparvovec is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from voretigene neparvovec therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data on the effect of the medicinal product on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Voretigene neparvovec has minor influence on the ability to drive and use machines. Patients may experience temporary visual disturbances after receiving subretinal injection of Luxturna. Patients should not drive or use heavy machines until visual function has recovered sufficiently, as advised by their ophthalmologist.

4.8 Undesirable effects

Summary of the safety profile

In the phase 1 and phase 3 clinical studies, there were three non-serious adverse reactions of retinal deposits in three of 41 (7%) subjects that were considered to be related to voretigene neparvovec. All three of these events were a transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site, 1-6 days after injection and resolved without sequelae.

Serious adverse reactions related to the administration procedure were reported in three subjects. One of 41 (2%) subjects reported a serious event of intraocular pressure increased (secondary to administration of depo-steroid) that was associated with treatment for endophthalmitis related to the administration procedure and resulted in optic atrophy, and one of 41 (2%) subjects reported a serious event of retinal disorder (loss of foveal function) that was assessed as related to the administration procedure. One of 41 (2%) subjects reported a serious event of retinal detachment that was assessed as related to the administration procedure.

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

Tabulated list of adverse reactions

The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data).

Table 2 Adverse reactions related to voretigene neparvovec

System organ class	Frequency	Adverse reaction
Eye disorders	Common	Retinal deposits
	Not known	Chorioretinal atrophy*
*Includes retinal degeneration, retinal depigmentation and injection site atrophy		

Table 3 Adverse reactions related to administration procedure

System organ class	Frequency	Adverse reactions
Psychiatric disorders	Common	Anxiety
Nervous system disorders	Common	Headache, dizziness
Eye disorders	Very common	Conjunctival hyperaemia, cataract
	Common	Retinal tear, dellen, macular hole, eye inflammation, eye irritation, eye pain, maculopathy, choroidal haemorrhage, conjunctival cyst, eye disorder, eye swelling, foreign body sensation in eyes, macular degeneration, endophthalmitis, retinal detachment, retinal disorder, retinal haemorrhage
	Not known	Vitreous opacities, chorioretinal atrophy*
Gastrointestinal disorders	Common	Nausea, vomiting, abdominal pain upper, lip pain
Skin and subcutaneous tissue disorders	Common	Rash, swelling face
Investigations	Very common	Intraocular pressure increased
	Common	Electrocardiogram T wave inversion
Injury, poisoning and procedural complications	Common	Endotracheal intubation complication, wound dehiscence
*Includes retinal degeneration, retinal depigmentation and injection site atrophy		

Description of select adverse reactions

Chorioretinal atrophy
Chorioretinal atrophy has been reported as an adverse reaction during post-marketing experience and reported as progressive in some patients. Events were temporally related to treatment and occurred in the estimated treated area of the bleb site and outside of the bleb area. Retinal atrophy may involve the fovea with possible negative effects on central vision.

Following reports of chorioretinal atrophy in the post-marketing setting, a retrospective review of fundus photographs available from 39 out of 41 patients enrolled in the clinical studies was performed.

In the phase 3 study, chorioretinal atrophy of the macula of treated eyes was found in 15.4% prior to treatment, in 42.6% at year 1 and in 55.6% after year 1. In the phase 1 study, chorioretinal atrophy of the macula was present in 35% prior to treatment, in 66.7% at year 1 and in 73.9% after year 1. Untreated control eyes showed the following rates of chorioretinal atrophy: 5.9% at baseline and 11.1% at year 1 in the phase 3 study; 40% at baseline, 42.9% at year 1 and 41.7% after year 1 in the phase 1 study.

Some of these atrophies involved the fovea. In the phase 3 study, there was involvement of the fovea in 1.9% of treated eyes prior to treatment, as well as at year 1, and in 5.6% after year 1. In the phase 1 study, the fovea was involved in 30% of treated eyes prior to treatment, in 38.9% at year 1 and in 47.8% after year 1. In the phase 3 study, atrophies in untreated control eyes did not involve the fovea. In the phase 1 study, 40% of atrophies in untreated control eyes involved the fovea at baseline, 42.9% at year 1 and 33.3% after year 1.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

There is no clinical experience with overdose of voretigene neparvovec. Symptomatic and supportive treatment, as deemed necessary by the treating physician, is advised in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other ophthalmologicals, ATC code: S01XA27.

Mechanism of action

The retinal pigment epithelium-specific 65 kilodalton protein (RPE65) is located in the retinal pigment epithelial cells and converts all-trans-retinol to 11-cis-retinol, which subsequently forms the chromophore, 11-cis-retinal, during the visual (retinoid) cycle. These steps are critical in the biological conversion of a photon of light into an electrical signal within the retina. Mutations in the *RPE65* gene lead to reduced or absent RPE65 all-trans-retinyl isomerase activity, blocking the visual cycle and resulting in vision loss. Over time, accumulation of toxic precursors leads to the death of retinal pigment epithelial cells, and subsequently to progressive photoreceptor cell death. Individuals with biallelic *RPE65* mutation-associated retinal dystrophy exhibit vision loss, including impaired visual function parameters such as visual acuity and visual fields often during childhood or adolescence; this loss of vision ultimately progresses to complete blindness.

Injection of voretigene neparvovec into the subretinal space results in transduction of retinal pigment epithelial cells with a cDNA encoding normal human RPE65 protein (gene augmentation therapy), providing the potential to restore the visual cycle.

Clinical efficacy and safety

The long-term safety and efficacy of Luxturna were assessed in a phase 1 safety and dose escalation study (101), in which 12 subjects received unilateral subretinal injections of voretigene neparvovec; a follow-on study (102) in which voretigene neparvovec was administered to the contralateral eye in 11 of the 12 subjects who participated in the dose escalation study; a one-year, open-label phase 3 controlled study (301) in which 31 subjects were randomised at two sites; and the continuation of the phase 3 study, in which the 9 control subjects crossed over and received the intervention. A total of 41 subjects (81 eyes injected [one phase 1 subject did not meet eligibility criteria for a second injection]) participated in the clinical programme. All participants had a clinical diagnosis of Leber congenital amaurosis, and some may have also had prior or additional clinical diagnoses, including retinitis pigmentosa. Confirmed biallelic *RPE65* mutations and the presence of sufficient viable retinal cells (an area of retina within the posterior pole of >100 micron thickness, as estimated by optical coherence tomography [OCT]) were established for all participants.

Phase 3 study
Study 301 was an open-label, randomised, controlled study. 31 subjects were enrolled, 13 males and 18 females. The average age was 15 years (range 4 to 44 years), including 64% paediatric subjects (n=20, age from 4 to 17 years) and 36% adults (n=11). All subjects had a diagnosis of Leber's congenital amaurosis owing to *RPE65* mutations confirmed by genetic analysis in a certified laboratory.

21 subjects were randomised to receive subretinal injection of voretigene neparvovec. Visual acuity (LogMAR) of the first eye of these subjects at baseline was 1.18 (0.14), mean (SE). One subject discontinued from the study prior to treatment. 10 subjects were randomised to the control (non-intervention) group. Visual acuity (LogMAR) of the first eye of these subjects at baseline was 1.29 (0.21), mean (SE). One subject in the control group withdrew consent and was discontinued from the study. The nine subjects who were randomised to the control group were crossed over to receive subretinal injection of voretigene neparvovec after one year of observation. Each eye was administered a single subretinal injection of 1.5×10^{11} vector genomes voretigene neparvovec in a total volume of 300 µL. The interval between injection to the eyes for each subject was from 6 to 18 days**.**

The primary endpoint of the phase 3 study measured the mean change from baseline to one year in binocular multi-luminance mobility testing (MLMT) between the intervention and control groups. The MLMT was designed to measure changes in functional vision, specifically the ability of a subject to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. This ability depends on the subject's visual acuity, visual field and the extent of nyctalopia (decreased ability to perceive and/or see in dim light), each of which are functions specifically affected by the retinal disease associated with *RPE65* mutations. In the phase 3 study, the MLMT used seven levels of illumination ranging from 400 lux to 1 lux (corresponding to, for example, a brightly lit office down to a moonless summer night). The testing of each subject was videotaped and assessed by independent graders. A positive change score reflects passing the MLMT at a lower light level and a lux score of 6 reflects the maximum possible MLMT improvement. Three secondary endpoints were also tested: full-field light sensitivity threshold (FST) testing using white light; the change in MLMT score for the first assigned eye; and visual acuity (VA) testing.

At baseline, subjects achieved pass marks on the mobility test at between 4 and 400 ambient lux.

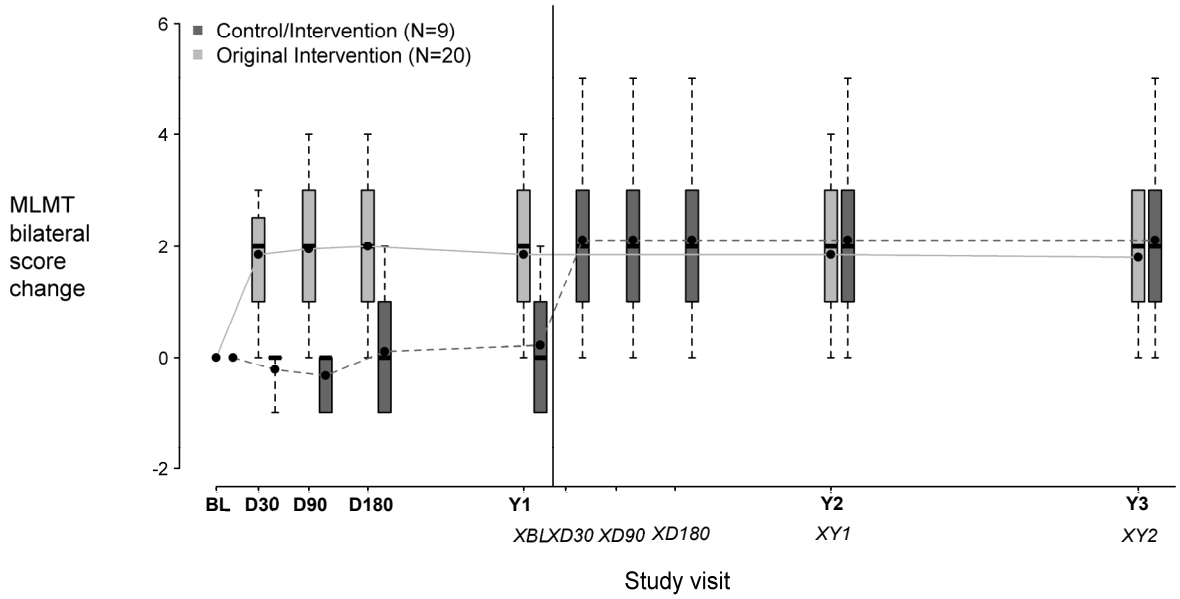
Table 4 Changes in MLMT score: year 1, compared to baseline (ITT population: n=21 intervention, n=10 control)

Change in MLMT score	Difference (95% CI) Intervention-Control	p-value
using binocular vision	1.6 (0.72, 2.41)	0.001
using assigned first eye only	1.7 (0.89, 2.52)	0.001
using assigned second eye only	2.0 (1.14, 2.85)	<0.001

The monocular MLMT change score significantly improved in the treatment group and was similar to the binocular MLMT results (see Table 4).

Figure 2 shows the effect of the medicinal product over the three-year period in the voretigene neparvovec treatment group, as well as the effect in the control group after crossing over to receive subretinal injection of voretigene neparvovec. Significant differences in binocular MLMT performance were observed for the voretigene neparvovec treatment group at day 30 and were maintained over the remaining follow-up visits throughout the three-year period, compared to no change in the control group. However, after crossing-over to receive subretinal injection of voretigene neparvovec, the subjects in the control group showed a similar response to the voretigene neparvovec as compared to the subjects in the voretigene neparvovec treatment group.

Figure 2 Change in MLMT score using binocular vision versus time before / after exposure to voretigene neparvovec



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. The dotted line connects the mean MLMT score change over visits for the control group, including five visits during the first year without receiving voretigene neparvovec. The control group was administered voretigene neparvovec after 1 year of observation.
BL: baseline;
D30, D90, D180: 30, 90 and 180 days after start of study;
Y1, Y2, Y3: one, two and three years after start of study;
XBL; XD30; XD90; XD180: baseline, 30, 90 and 180 days after start of study for control crossover group;
XY1; XY2: one and two years after start of study for control crossover group.

Results of full-field light sensitivity testing at the first study year: white light [Log10(cd.s/m^2)] are shown in Table 5 below.

Table 5 Full-field light sensitivity testing

Full-field light sensitivity testing – First assigned eye (ITT)			
	Intervention, N = 21		
	Baseline	**Year 1**	**Change**
N	20	20	19
Mean (SE)	-1.23 (0.10)	-3.44 (0.30)	-2.21 (0.30)
	Control, N = 10		
N	9	9	9
Mean (SE)	-1.65 (0.14)	-1.54 (0.44)	0.12 (0.45)
	Difference (95% CI) (Intervention-Control) -2.33 (-3.44, -1.22), p<0.001		
Full-field light sensitivity testing – Second assigned eye (ITT)			
	Intervention, N = 21		
	Baseline	**Year 1**	**Change**
N	20	20	19
Mean (SE)	-1.35 (0.09)	-3.28 (0.29)	-1.93 (0.31)
	Control, N = 10		
N	9	9	9
Mean (SE)	-1.64 (0.14)	-1.69 (0.44)	0.04 (0.46)
	Difference (95% CI) (Intervention-Control) -1.89 (-3.03, -0.75), p=0.002		
Full-field light sensitivity testing - Averaged across both eyes (ITT) Difference (95% CI) (Intervention-Control): -2.11 (-3.19, -1.04), p<0.001			

Improvement in full-field light sensitivity was maintained for up to 3 years after exposure to voretigene neparvovec.

At one year after exposure to voretigene neparvovec, improvement in visual acuity of at least 0.3 LogMAR occurred in 11/20 (55%) of the first-treated eyes and 4/20 (20%) of the second-treated eyes in the intervention group; no one in the control group displayed such an improvement of visual acuity in either the first or second eye.

5.2 Pharmacokinetic properties

Voretigene neparvovec is expected to be taken up by cells through heparin sulphate proteoglycan receptors and be degraded by endogenous proteins and DNA catabolic pathways.

Non-clinical biodistribution

Biodistribution of voretigene neparvovec 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 stomach and lymph nodes. In one animal administered with voretigene neparvovec at 7.5×10^{11} vector genomes (5 times the recommended per eye dose), vector DNA sequences were detected in colon, duodenum and trachea. Vector DNA sequences were not detected in gonads.

Clinical pharmacokinetics and shedding

The vector shedding and biodistribution were evaluated in tears from both eyes, serum and whole blood of subjects in the phase 3 clinical study. In 13/29 (45%) subjects receiving bilateral administrations, voretigene neparvovec vector DNA sequences were detected in tear samples; most of these subjects were negative after the day 1 post-injection visit, however, four of these subjects had positive tear samples beyond the first day, one subject up to day 14 post-second eye injection. Vector DNA sequences were detected in serum in 3/29 (10%) subjects, including two with positive tear samples, and only up to day 3 following each injection. Overall, transient and low levels of vector DNA were detected in tear and occasional serum samples from 14/29 (48%) of subjects in the phase 3 study.

Pharmacokinetics in special populations

No pharmacokinetic studies with voretigene neparvovec have been conducted in special populations.

Hepatic and renal impairment
Luxturna is injected directly into the eye. Liver and kidney function, cytochrome P450 polymorphisms and ageing are not expected to influence the clinical efficacy or safety of the product. Therefore, no adjustment in dose is necessary for patients with hepatic or renal impairment.

5.3 Preclinical safety data

Ocular histopathology of dog and non-human primate eyes exposed to voretigene neparvovec showed only mild changes, which were mostly related to healing from surgical injury. In an earlier toxicology study, a similar AAV2 vector administered subretinally in dogs at a dose of 10 times the recommended dose resulted in focal retinal toxicity and inflammatory cell infiltrates histologically in regions exposed to the vector. Other findings from voretigene neparvovec non-clinical studies included occasional and isolated inflammatory cells in the retina, with no apparent retinal degeneration. Following a single vector administration, dogs developed antibodies to the AAV2 vector capsid which were absent in naïve non-human primates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate

Sodium chloride
Sodium dihydrogen phosphate monohydrate (for pH adjustment)
Disodium hydrogen phosphate dihydrate (for pH adjustment)
Poloxamer 188
Water for injections

Solvent

Sodium chloride
Sodium dihydrogen phosphate monohydrate (for pH adjustment)
Disodium hydrogen phosphate dihydrate (for pH adjustment)
Poloxamer 188
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened frozen vials

3 years

After thawing

Once thawed, the medicinal product should not be re-frozen and should be left at room temperature (below 25 °C).

After dilution

Following dilution under aseptic conditions, the solution must be used immediately; if not used immediately, the storage time at room temperature (below 25 °C) should be no longer than 4 hours.

6.4 Special precautions for storage

Concentrate and solvent must be stored and transported frozen at ≤-65 ºC.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Concentrate

0.5 mL extractable volume of concentrate in 2 mL cyclic olefin polymer vial with a chlorobutyl rubber stopper sealed in place with an aluminium flip-off seal.

Solvent

1.7 mL extractable volume of solvent in a 2 mL cyclic olefin polymer vial with a chlorobutyl rubber stopper sealed in place with an aluminium flip-off seal.

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

6.6 Special precautions for disposal and other handling

Precaution 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.

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.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1331/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2018
Date of latest renewal: 24 July 2023

10. DATE OF REVISION OF THE TEXT

04/2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.