Date: 15 April 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

LUXTURNA

International non-proprietary name: Voretigene neparvovec
Pharmaceutical form: Concentrate and solvent for solution for injection
Dosage strength: 1.5 x 10^{11} vg / 0.3 mL
Route(s) of administration: Subretinal injection
Marketing Authorisation Holder: Novartis Pharma Schweiz AG
Marketing Authorisation No.: 67371
Decision and Decision date: approved on 14 February 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

AAV2	Adeno-associated virus serotype 2
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
ERG	Electroretinogram
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
Max	Maximum
MAH	Marketing Authorisation Holder
Min	Minimum
MLMT	Multi-luminance mobility test
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PSP	Paediatric Study Plan (US-FDA)
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
RMP	Risk Management Plan
RPE65	Retinal pigment epithelium-specific 65 kilodalton protein
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
Vg	Vector genome

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2 Background Information on the Procedure

2.1 Applicant's Request

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 9 July 2019.

2.2 Indication and Dosage

2.2.1 Requested Indication

Luxturna is used 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.

2.2.2 Approved Indication

Luxturna is used 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.

2.2.3 Requested Dosage

Treatment should be initiated and administered by a retinal surgeon experienced in performing macular surgery.
Patients receive a single dose of 1.5 x 10^{11} vg Luxturna in each eye. Each dose is 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.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	10 May 2019
Formal control completed	14 May 2019
List of Questions (LoQ)	18 July 2019
Answers to LoQ	7 October 2019
Predecision	26 November 2019
Answers to Predecision	27 January 2020
Final Decision	14 February 2020
Decision	approval

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2.4 Medical Context

Biallelic mutations in the RPE65 gene are responsible for Leber's congenital amaurosis (LCA) type 2, as well as for some cases of retinitis pigmentosa (RP) and other clinical diagnoses of inherited retinal dystrophy.
There is currently no medicinal product on the market for patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations. Treatment is generally supportive; affected individuals benefit from correction of refractive error and use of low-vision aids.
Surgical devices are available for some subjects who meet clinical requirements: either the Argus® II Retinal Prosthesis System or the Alpha AMS Retina Implant AG. The devices have variable and limited clinical efficacy. Consequently, there is an unmet clinical need for this condition.
Luxturna (voretigene neparvovec) is an adeno-associated viral serotype 2 (AAV2) gene therapy vector containing a cDNA encoding functional human RPE65 protein. Administration by single injection into the subretinal space of the eye results in transduction of some of the retinal pigment epithelial cells with cDNA encoding the RPE65 protein. Subsequent expression of the RPE65 protein, all-trans-retinyl isomerase, then permits the regeneration of 11-cis-retinal in photoreceptor cells and can thus lead to improvements in the ability to detect light.

3 Quality Aspects

3.1 Drug Substance

Voretigene neparvovec, the active substance of Luxturna, is an *in vivo* gene transfer vector derived from naturally occurring adeno-associated virus, serotype 2 (AAV2), for delivery of the functional human retinal pigment epithelium-specific 65 kDa protein (hRPE65) gene into the retinal pigment epithelium. Virus capsid consists of viral capsid proteins assembled in an icosahedral structure, and serves as a delivery vehicle for the transgene. Wild-type vector genome, with the exception of flanking inverted terminal repeats (ITRs), is replaced by the therapeutic transgene expression cassette using recombinant DNA techniques.
Wild-type AAV2 virus is non-pathogenic, and naturally replication-deficient, requiring co-infection with helper virus in order to replicate.
Voretigene neparvovec is produced in a well-established mammalian cell line after transient transfection with a mixture of three plasmids carrying genes for components of the viral capsid, helper virus proteins and transgene. Characterisation of the three recombinant plasmids and their production in bacterial cell banks have been described, and their specifications were provided. During the production of voretigene neparvovec, the cells from one vial of the cell bank are expanded, transfected and harvested. The cell harvest is further purified by several chromatographic and filtration steps, then formulated and filled into the primary container closure system. Voretigene neparvovec as a drug substance is a clear and colourless solution of viral particles in the formulation buffer.
The process performance qualification run was performed, and the manufacturing process was demonstrated to operate consistently.
Voretigene neparvovec drug substance and its impurities were sufficiently characterised using state-of-the-art analytical methods.
The specification tests and acceptance criteria are provided, and include e.g. identity tests, purity and impurity testing, and cell-based potency assays. Analytical methods are described, and non-compendial methods have been validated in accordance with ICH guidelines.
Batch data analysis from clinical and engineering batches as well as a process performance qualification batch and two commercial batches were provided. Comparability between the clinical batch used for the Phase III study and the batches produced with the commercial process at a new manufacturing site was demonstrated.
The shelf-life proposed for the drug substance stored at ≤ -65 °C in the original container was accepted.

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3.2 Drug Product

The Luxturna drug product is supplied as a solution for injection of $5x10^{12}$ vector genomes per mL (corresponding to 0.05 mg vector per mL) in a volume of 0.5 mL in a 2 mL Crystal Zenith vial (cyclic olefin polymer) with a chlorobutyl rubber stopper sealed with an aluminium flip-off seal. The finished product is formulated as a concentrate requiring a 1:10 dilution with the solvent supplied. After dilution, 0.3 mL are administered into one eye, corresponding to the dose of $1.5x10^{11}$ total vector genome per treatment. The formulation of the concentrate is an aqueous buffered solution containing sodium chloride, sodium phosphate and poloxamer 188. The solvent is an aqueous buffered solution containing sodium chloride, sodium phosphate and poloxamer 188. The excipients comply with the pharmacopoeia.
The drug product after dilution is intended for subretinal injection. It is for single use only and is preservative free.
The manufacturing process for the finished product consists of the thawing of the drug substance aliquots, followed by sterile filtration and filling into the final containers. No change in formulation from drug substance to drug product is introduced. The process performance qualification was performed at a commercial scale for the manufacture of concentrate and solvent and included filter validation and aseptic process validation, as well as shipping validation. Comparability between clinical batch and commercial process qualification batch was shown.
The specification tests and acceptance criteria are provided and include relevant tests such as appearance, colour of solution, pH, osmolality, particulate matter, identity, concentration and purity, cell-based potency assays, endotoxins, sterility. Analytical methods are described, and non-compendial methods have been validated in accordance with ICH requirements.
Batch data from the process performance qualification batch met the commercial product release specification.
The drug product, concentrate and solvent, is stored at ≤ -65 °C in original, unopened containers. A shelf-life of 24 months has been accepted. The proposed in-use shelf-life after dilution of 4 hours at room temperature is supported by an in-use stability study.
The manufacturing processes for the drug substance and drug product incorporate adequate control measures to prevent contamination and maintain control with regard to viral and non-viral contaminants.

3.3 Quality Conclusions

The manufacturing processes for the drug substance and the drug product are well described and indicate a consistent quality of drug substance and drug product. The shelf-lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as from accelerated and stress studies. Safety concerns with regard to viral and non-viral contamination were satisfactorily addressed.

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4 Nonclinical Aspects

Pharmacodynamic aspects

AAV2-hRPE65v2 (voretigene neparvovec) is a replication-defective adeno-associated viral (AAV) vector derived from the AAV2 serotype. It codes for the human retinal pigment epithelium-specific protein RPE65. The RPE65 cDNA is cloned between the two AAV inverted terminal repeats (ITR), and the expression is driven by the cytomegalovirus (CMV) enhancer and the chicken beta actin (CβA) promoter. The RPE65 cDNA codes for all-trans-retinyl-isomerase, is expressed in retinal pigment epithelial cells and is involved in the conversion of all-trans retinal back to 11-cis-retinal (retinal cycle). Mutations in RPE65 cause Leber's congenital amaurosis type 2 (LCA2) and some cases of retinitis pigmentosa (RP).

In vitro, AAV-hRPE65v2 was characterised in canine primary normal and mutant RPE cells and in human HEK/293 cells in culture. Expression of RPE65 transgene was shown after transduction of cells with the AAV2-RPE65 viral vector, as measured by polymerase chain reaction (PCR), Western-blot and immunohistochemical analyses.

In vivo, two mouse models (Rpe65-/- mice and Rd12 mice) with disrupted RPE65 genes were used. Subretinal injections of up to 1 x 10^9 AAV-hRPE65v2 viral vector genomes (vg) resulted in the expression of RPE65 mRNA and protein in RPE cells, and improved ERG patterns and visual acuity were measured. In addition to mice, AAV-hRPE65v2 was also investigated in Briard dogs. These dogs harbour an autosomal recessive mutation in the *Rpe65* gene (4 base pair deletion at position 485). This deletion leads to a frameshift and generation of a stop codon, resulting in a truncated, non-functional RPE65 protein. Affected dogs display reduced night vision, rod outer segment distortions in the retina, nystagmus and low amplitude b-waves in the ERG. Subretinal injection of up to 4.6 x 10^{10} vg of AAV-hRPE65v2 viral vectors resulted in improved visual behaviour (improved ERG and pupillary responses, reduced nystagmus, improved ability of dogs to navigate through an obstacle course). Reverse transcription PCR (RT-PCR) analysis confirmed *Rpe65* mRNA expression in retinal tissue, and the treatment resulted in RPE65 protein expression and the disappearance of vacuoles in the RPE of the treated areas. In addition, 11-*cis*-retinal formation was measured in treated areas. Long-term activity in dogs was reported for up to 11 years. No dose-finding studies were performed in vivo.

Biodistribution

The biodistribution (BD) was well characterised in vivo in two different species (dogs, non-human primates). In dogs, 3 weeks and 3 months after subretinal injection of 1.5 x 10^{12} vg, qPCR assays identified viral vector sequences in vitreous fluid, anterior chamber fluid, preauricular lymph nodes and optic nerve. In dogs, technical difficulties precluded the identification of viral vector sequences in the liver and lung by quantitative PCR (qPCR). In non-human primates, in addition to the eye and optic nerve, viral vector DNA was also detected in various lymph nodes, the colon, duodenum, stomach, liver, spleen and trachea. No gonadal tissues were positive for AAV-hRPE65 viral vectors. The assay sensitivity was at 10 copies/μg DNA, which can be considered as adequate for measuring the distribution of the viral vector genome in several tissues of dogs and monkeys.

Toxicology

The safety of AAV2-hRPE65 was assessed in single and repeat dose studies in dogs (3 weeks, 3 months) and non-human primates (3 months). Although the study in non-human primates was not performed according to GLP, it was performed at a sufficiently high standard to allow an adequate assessment of the toxicity. The safety profile can be considered acceptable, with most effects localised to the treated eye. Some adverse events seem more related to the surgical procedure than to the vector application (i.e. scarring near injection sites). In dogs, subretinal injections of up to 1.5 x 10^{12} vg were used, which represents 10x the clinical dose. Signals in the toxicity evaluation of AAV2-hRPE65 in dogs included perivascular lymphocyte cuffing in the brain stem and midbrain in the 3-week dog study. No perivascular lymphocyte cuffing was observed in the 3-month dog study. No toxic effects were observed at dose levels lower than 1.5 x 10^{12} vg. Signals in the brain stem and

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midbrain were absent in the monkeys at all dose levels tested (up to 7.5 x 10^{11} vg). Immune reactions to the viral vector and the encoded transgene were determined. Whereas humoral responses to the viral capsid protein were detected, antibody formation towards human RPE65 was minimal. T-cell responses (especially CD8-dependent responses) were generally absent in dogs and non-human primates. No studies have evaluated carcinogenicity, genotoxicity or reproductive toxicity. Based on the nature of the AAV2-hRPE65v2 (voretigene neparvovec) viral vector, this can be considered acceptable as no effects are expected.

Nonclinical Conclusions

The submitted nonclinical data support the proposed mechanism of action of subretinal administration of AAV2-hRPE65v2. The biodistribution and safety evaluations of AAV2-hRPE65v2 are sufficient. No safety issues were identified that would preclude the approval of the application. Shedding data were not evaluated nonclinically. However, submitted clinical data with respect to shedding are considered adequate and sufficient. Based on the submitted documentation and the responses to the questions asked by the Regulatory Authority, this application is approvable from a nonclinical perspective.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

The available assessment reports and respective product information from the EMA and the USFDA were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, see Chapter 7.1 of this report.

5.2 Dose Finding and Dose Recommendation

The final selection of the dose level employed (1.5×10^{11} vg in 0.3 mL per eye) was based on the results of the Phase 1 studies 101 and 102 (AAV2-hRPE65v2-101 and AAV2-hRPE65v2-102).
In study AAV2-hRPE65v2-101 (Study 101), twelve subjects aged 8 to 44 received unilateral subretinal injections of voretigene neparvovec. There were three dose cohorts:
Low dose 1.5×10^{10} vg in 0.15 mL in 1 male and 2 female subjects
Middle dose 4.8×10^{10} vg in 0.15 mL in 4 male and 2 female subjects
High dose 1.5×10^{11} vg in 0.30 mL in 2 male and 1 female subjects

In study 102, voretigene neparvovec was administered at the dose of 1.5×10^{11} vg in 0.3 mL to the contralateral eye in 11 of the 12 subjects who participated in the initial dose escalation study 101.

A dose of 1.5×10^{11} vg in a volume of 300 µL per eye was determined to be safe and well tolerated. As all doses had similar safety profiles, the high dose was adopted. A dose-response effect could be neither established nor eliminated due to phenotypic variations of the subjects enrolled. In the absence of a dose-response effect, the volume of 300 µL utilised for the Phase 1 high-dose cohort was considered likely to target a larger portion of the retina and thus to provide a greater likelihood of benefit to the subjects.

5.3 Efficacy

The long-term safety and efficacy data for Luxturna were assessed in the Phase 1 safety and dose escalation study 101, in the contralateral eye study 102, and in the pivotal, one-year, open-label, Phase 3 controlled study (301).

A total of 41 subjects (81 eyes) were injected during the clinical development programme. Biallelic RPE65 mutations confirmed by genetic analysis in a certified laboratory 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. Each eye was administered a single subretinal injection of 1.5×10^{11} vg voretigene neparvovec in a total volume of 300 µL. In the pivotal study 301, the interval between injection to the eyes for each subject was from 6 to 18 days.

The pivotal 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, aged from 4 to 17 years) and 36% adult subjects (n=11). The 31 subjects (21 intervention, 10 control) were randomised, with a stratification by age (≥ 10 years or < 10 years) and by mobility testing category (passing at ≥ 125 lux or passing at < 125 lux).

A mobility test developed by Spark Therapeutics specifically for the Luxturna study, the multi-luminance mobility test (MLMT), was used as the primary endpoint. This test has been described in the publication by Daniel C. Chung et al, "*Novel Mobility Test to Assess Functional Vision in Patients with Inherited Retinal Dystrophies*", in the Journal of Clinical and Experimental Ophthalmology (2018). The MLMT score measures changes in functional vision, specifically the ability to navigate a course at different levels of light.

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To quantify subject performance over time, an MLMT change score algorithm was developed. Each light level evaluated during the study was assigned a score ranging from 0 to 6. A higher score indicated that a patient was able to pass the MLMT at a lower light level. The phase 3 study evaluated subjects at seven light levels (1, 4, 10, 50, 125, 250 and 400 lux). The MLMT change score was determined using the difference in score code from the baseline lower light sensitivity cut-off (i.e. the lowest light level at which a subject passed the course) to the lower light sensitivity cut-off at the one-year visit.

The MLMT was evaluated by masked assessors who had no knowledge of treatment assignment or knowledge of the timing of the MLMT.
At baseline, subjects scored pass marks in the mobility test at between 4 and 400 ambient lux, i.e. there was much variation between subjects in visual competence.

The primary objective of the Phase 3 pivotal study 301 was to determine whether non-simultaneous, bilateral subretinal administration of AAV2-hRPE65v2 improved the bilateral performance (no eye patching) on the mobility test (MLMT), as measured by the change score, one year following vector administration, as compared to the subject's baseline. A positive change score reflects passing the MLMT at a lower light level. The primary efficacy endpoint of the Phase 3 pivotal study 301 thus measured the mean change from baseline to one year in the binocular multi-luminance mobility test (MLMT) between the intervention and control groups.

Intervention group: 21 ITT (safety), 20 mITT (modified intention to treat)
Control group: Crossover to intervention group after primary endpoint reached at one year for intervention group.
Crossover group: n=10 ITT, 9 mITT (one patient in each group discontinued, or was withdrawn, prior to treatment with Luxturna).

The analysis of the bilateral MLMT score changes in the intention-to-treat population (ITT) showed a statistically significant mean group difference of 1.6 (95% confidence interval [CI] of 0.72, 2.41; p = 0.001).

For more information on the change in functional vision (MLMT results, primary endpoint), see the tables in the information for healthcare professionals, one of which is replicated here:

Magnitude of MLMT Score Change Using Both Eyes at Year 1

Score Change	Luxturna (n=21)	Control (untreated) (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

Note that eight patients (38%) in the Luxturna group had an MLMT score change of one, while three patients in the control group (30%) also had an MLMT score change of one. An MLMT score change of one may therefore be due to background fluctuation, while an MLMT score change of > 2 can be considered a clinically relevant improvement.

Thus, about 50% of patients treated with Luxturna showed a net benefit, while some of the others were stabilised. In the control group, before crossover, only one subject (about 10%) showed a net benefit, three (30%) showed continued loss of vision and 60% seemed to remain stable without Luxturna treatment. Given the high variability of differences in the types of mutation leading to RPE65

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deficiency and the high variability of phenotypic presentations and natural history of inherited retinal dystrophies caused by biallelic RPE65 mutations, as well as the wide range of patients, this range of results is probably to be expected. Due to the small size of the studies, baseline prognostic factors could not be established.

Key secondary efficacy outcomes were full-field sensitivity threshold (FST) testing (light sensitivity), monocular mobility testing change score (as compared to binocular testing in the primary endpoint) and visual acuity (VA) (change in visual acuity as averaged over both eyes), all at year 1 as compared to baseline. Overall, the results supported the primary endpoint results, although, as for the primary endpoint, some but not all treated subjects benefitted.

5.4 Safety

Overall, 9 of 81 (11%) eyes and 7 of 41 (17%) subjects in the clinical programme reported one macular disorder event (macular hole, maculopathy, foveal thinning, foveal dehiscence). All events were considered to be related to the administration procedure. In one patient there was a permanent loss of foveal function in one eye.

Intraocular inflammation was reported in 5 of 81 (6%) eyes and 3 of 41 (7%) subjects in the clinical programme, including one episode in one eye (1/81, 1%) of intraocular infection (culture-positive endophthalmitis). All events were considered to be related to the procedure.

One of 81 (1%) eyes in one of 41 (2%) subjects administered voretigene neparvovec in the clinical programme had a retinal detachment. The retinal detachment was reported four years after the administration procedure, and was considered to be related to the procedure.

Note that a majority of patients experience adverse events after receiving Luxturna, either due to the surgical procedure (anaesthesia, endotracheal tube, vitrectomy, subretinal injection, use of steroids), or to ocular adverse reactions following the procedure. These adverse events include, in addition to those mentioned above, increased intraocular pressure, cataracts, retinal tear, retinal haemorrhage, eye pain, eye pruritus and conjunctival hyperaemia. The information for healthcare professionals should be consulted for a full list and information on the expected frequency. The majority of adverse events are known complications of intraocular surgery, and most occurred during the year post-administration. Several of these adverse events are, or can be, potentially serious and / or severe, and could affect the efficacy (or lack of efficacy) of Luxturna.

5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

From the data available so far, at least half of the patients showed a clinically relevant benefit from the treatment with Luxturna, in terms of the ability to function better at lower light levels and to maintain a larger field of vision. Halting further progression of the disease is also likely to be of benefit, even in those with advanced disease.

Based on the currently available follow-ups, the effect seems to last for at least three to four years. These observations, together with the severity and progressive nature of the disease and the current lack of pharmacological treatment options, clearly speak for a marketing authorisation. Up to now, the clinical management for biallelic RPE65 mutations has been supportive only. Low-vision aids, orientation and mobility training, and medical devices have been the only available options.

Whether the effect of Luxturna can be upheld for many years and prevent blindness in the long term remains open. A 15-year follow-up of the 41 clinical programme patients is ongoing, and a five-year post-marketing PASS study (Post-Authorisation Safety Study) was required as a condition for marketing authorisation.

Other remaining uncertainties include the lack of knowledge regarding those baseline factors that might influence the benefit-risk profile of Luxturna. There was insufficient power in the clinical trials to

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determine whether the age or gender of the patient, stage of disease, pre-treatment speed of vision decline, type of biallelic RPE65 mutation, and other patient or disease characteristics may constitute prognostic factors for the efficacy, or lack of efficacy, of Luxturna. Those with less degeneration (i.e. more viable retinal cells) seemed to benefit to a greater degree.

The determination of prognostic factors would be important given that the unfavourable effects (risks) are high due to the subretinal injection procedure needed in order to administer Luxturna. These events can be serious and cause permanent loss of vision. A long-term thorough follow-up by specialised ophthalmologists and patient education are therefore essential.

In order to ensure optimal follow-up of patients and to allow surgeons to have sufficient, regular experience with the application of Luxturna, only category A1 university hospitals are allowed to administer Luxturna, and even then only after appropriate training.

Taking into consideration all of the above points, the benefit-risk profile of voretigene neparvovec was determined to be positive.

5.6 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to LUXTURNA was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See "Adverse effects" for information on reporting adverse effects.

Luxturna®

Composition

Active substances

Voretigene neparvovec: 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-specific 65 kDa protein (hRPE65) cDNA to the retina. Voretigene neparvovec is derived from naturally occurring AAV using recombinant DNA techniques.
Consists of a genetically modified adeno-associated viral vector serotype 2 (AAV2).

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.

Pharmaceutical form and quantity of active substance per unit

Concentrate and solvent for solution for injection. The concentrate for subretinal injection is available in a 2 ml single-dose vial with an extractable volume of 0.5 ml. The concentration [5×10^{12} vector genomes (vg) per ml] requires a 1:10 dilution prior to administration.

After dilution one dose contains 1.5×10^{11} vg in a deliverable volume of 0.3 ml.

The solvent is supplied in two single-use vials each containing 2 ml and an extractable volume of 1.7 ml.

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

Indications/Potential uses

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

Dosage/Administration

Before treatment with Luxturna the presence of a biallelic *RPE65* mutation and the type of mutation must be established by a validated test. This test falls under the scope of the Federal Act on Human

Genetic Testing (GUMG) and can only be ordered from a laboratory approved for this specialist field by the Federal Office of Public Health (BAG).

Luxturna may only be used in category A1 university hospitals. These must have a qualified eye treatment centre with experience in the care and treatment of patients with inherited retinal dystrophy and a specialised hospital pharmacy. Doctors and pharmacists must be trained in the use and preparation of Luxturna. Treatment must be initiated and performed by a trained retinal surgeon experienced in performing macular surgery.

Patients receive a single dose of 1.5×10^{11} vg of Luxturna per eye. Each dose is delivered into the subretinal space in a total volume of 0.3 ml. Luxturna must not be administered as an intravitreal injection. Individual administration to each eye is performed on separate days within a close interval, but no fewer than 6 days apart.

For more detailed information on the preparation, administration and disposal of Luxturna see "Instructions for use and handling".

Immunomodulatory regimen

Prior to initiation of the immunomodulatory regimen and prior to administration of Luxturna the patient must be checked for symptoms of active infectious disease of any nature. If such an infection is present, the start of treatment must be postponed until the patient has recovered.

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

Table 1 Pre- and postoperative immunomodulatory regimen

Preoperative	3 days prior to Luxturna administration	Prednisone (or equivalent) 1 mg/kg/day (maximum daily dose: 40 mg)
Postoperative	4 days (including the day of Luxturna administration)	Prednisone (or equivalent) 1 mg/kg/day (maximum daily dose: 40 mg)
	Followed by 5 days	Prednisone (or equivalent) 0.5 mg/kg/day (maximum daily dose: 20 mg)
	Followed by 5 days of one dose every other day	Prednisone (or equivalent) 0.5 mg/kg every other day (maximum daily dose: 20 mg)

To ensure traceability of medicinal products containing genetically modified organisms, the trade name and batch number must be documented for every treatment.

Special populations

Patients with hepatic or renal impairment

The safety and efficacy of Luxturna in patients with hepatic or renal impairment have not been established. No dose adjustment is required in these patients (see “Pharmacokinetics in special populations”).

Elderly patients (65 years of age or over)

The safety and efficacy of Luxturna in patients aged 65 years and over have not been established.

Children and adolescents (under 18 years of age)

The safety and efficacy of Luxturna in children under 4 years of age have not been established. No dose adjustment is required for paediatric patients over 4 years of age.

Use in infants aged under 12 months is not recommended as there is a risk of possible dilution or loss of Luxturna after administration due to the active proliferation of retinal cells that occurs in this age group.

Contraindications

- Ocular or periocular infection.
- Active intraocular inflammation.
- Hypersensitivity to the active substance or any of the excipients.

Warnings and precautions

Endophthalmitis

Endophthalmitis may occur following any intraocular surgical procedure or injection. Always use proper aseptic injection technique when administering Luxturna. Following the injection patients must be monitored to permit early treatment in the event of infection. Patients must be instructed to report any signs or symptoms of infection or inflammation without delay.

Permanent decline in visual acuity

A permanent decline in visual acuity may occur following subretinal injection of Luxturna. Monitor patients for visual disturbances.

Retinal disorders

Retinal disorders may occur during or following the subretinal injection of Luxturna, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence and retinal haemorrhage. Monitor and manage these retinal disorders accordingly. Do not administer Luxturna in the immediate vicinity of the fovea (see "Instructions for use and handling").

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

Increased intraocular pressure

Increased intraocular pressure may occur after subretinal injection of Luxturna. Monitor and manage intraocular pressure accordingly.

Expansion of intraocular air bubbles

Instruct patients to avoid air travel, travel to high elevations and scuba diving until the air bubbles formed following administration of Luxturna, which may enter the eye, have completely dissipated. Dissipation of the air bubble may take up to one week or more following injection. Verify the dissipation of the air bubble through ophthalmic examination. A rapid increase in altitude while the air bubble is still present can cause a rise in intraocular pressure and irreversible vision loss.

Temporary visual disturbances such as blurred vision and photophobia may occur during the weeks following treatment. Patients should be instructed to consult their ophthalmologist if visual disturbances persist. Patients should avoid swimming because of an increased risk of eye infection. Patients should avoid strenuous physical activity because of an increased risk of injury to the eye. With the agreement of their doctor patients may resume swimming and strenuous physical activity after a minimum of one to two weeks.

Vector shedding

Transient and low-level vector shedding may occur in patient lacrimal fluid (see "Pharmacokinetics"). As a precautionary measure patients/caregivers should be instructed to handle waste generated from dressings, lacrimal fluid and nasal secretion appropriately. This may also include storage of waste material in sealed bags prior to disposal. These handling precautions are to be followed for 14 days after administration of Luxturna. Patients/caregivers are recommended to wear gloves for dressing changes and waste disposal. This applies particularly to pregnant, breast-feeding or immunodeficient caregivers.

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

Cataract

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

Immunogenicity

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

Interactions

No interaction studies have been performed.

Pregnancy/Breast-feeding

Considering the subretinal route of administration of Luxturna and based on non-clinical and clinical data from studies with AAV2 vectors, there is a very low or negligible risk of inadvertent transmission of AAV vectors into the germ line.

Pregnancy

There are no adequate and well-controlled studies in pregnant women to inform a medicinal product-associated risk. Animal reproductive studies have not been conducted with voretigene neparvovec.

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

Breast-feeding

It is not known whether voretigene neparvovec is excreted in human milk. There are no data on the effects of voretigene neparvovec on the breast-fed infant or milk production. A decision must be made whether to discontinue breast-feeding or to abstain from treatment with voretigene neparvovec, taking into account both the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

There are no data on the effects of the medicinal product on fertility.

Effects on ability to drive and use machines

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

Adverse effects

Summary of the safety profile

Three non-serious adverse drug reactions in the form of retinal deposits occurred in three of 41 (7%) patients that were assumed 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 that occurred 1 to 6 days after injection and resolved without sequelae.

Serious adverse drug reactions related to the administration procedure occurred in three patients during the clinical development programme. One of 41 patients (2%) reported increased intraocular pressure as a serious event (secondary to administration of a depo-steroid) that was associated with treatment for endophthalmitis; this occurred in connection with the administration procedure and resulted in atrophy of the optic nerve. Retinal disorder (loss of foveal function) and retinal detachment were each reported in one patient (1/41; 2%).

The most common adverse drug reactions related to the administration procedure (incidence ≥5%) were conjunctival hyperaemia, cataract, increased intraocular pressure, retinal tear, corneal 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).

Summary of adverse drug reactions from clinical studies

The safety data described in this section reflect exposure to voretigene neparvovec in three clinical studies in 41 patients (81 treated eyes) with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutation. Study 101 (n=12) was a phase 1 safety and dose escalation study in which 12 patients received unilateral subretinal injections of voretigene neparvovec. Eleven of the twelve subjects who participated in the dose escalation study received voretigene neparvovec in the second eye (Study 102). Study 301 (n=29) was an open-label, randomised, controlled study of efficacy and safety (see "Clinical efficacy"). In total, 40 of the 41 patients received sequential subretinal injections of voretigene neparvovec in each eye. One patient received voretigene neparvovec in only one eye.

72 of the 81 eyes were treated with the recommended dose of Luxturna of 1.5 x 10^{11} vg. In Study 101, 9 eyes were treated with a lower dose of voretigene neparvovec. The average age of the 41 patients was 17 years. Ages ranged from 4 to 44 years. Of the 41 patients, 25 (61%) were paediatric patients under 18 years of age and 23 (56%) were females.

Adverse drug reactions from clinical studies (Studies 101, 102 and 301, 41 patients in total) are listed by MedDRA system organ class. Within each system organ class the adverse drug reactions are listed by frequency, with the most frequent adverse drug frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the

corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

The adverse drug reactions may be related to voretigene neparvovec, the subretinal injection procedure, the concomitant use of corticosteroids or a combination of these procedures and medicinal products.

Table 1 Percentage of patients with adverse drug reactions in clinical studies

Frequency group	**Adverse drug reactions**	**Studies 101 + 102 + 301 (N=41 subjects)* n (%)**
Eye disorders		
Very common	Conjunctival hyperaemia[a]	9 (22)
	Cataract	8 (20)
Common	Retinal tear[g]	*4 (10)*
	Macular hole	*3 (7)*
	Retinal deposits[b]	*3 (7)*
	Corneal dellen	*3 (7)*
	Eye inflammation	2 (5)
	Maculopathy[c]	2 (5)
	Eye irritation	2 (5)
	Eye pain	2 (5)
	Retinal detachment	1 (2)
	Retinal haemorrhage	1 (2)
	Choroidal haemorrhage	1 (2)
	Endophthalmitis	1 (2)
	Macular degeneration[d]	1 (2)
	Conjunctival cyst	1 (2)
	Eye disorders[e]	1 (2)

	Eye swelling	1 (2)
	Foreign body sensation in the eyes	1 (2)
	Retinal disorder [f]	1 (2)
Investigations		
Very common	Increased intraocular pressure	6 (15)
Common	Electrocardiogram T wave inversion	1 (2)
Psychiatric disorders		
Common	Anxiety	1 (2)
Nervous system disorders		
Common	Headache	3 (7)
	Dizziness	1 (2)
Gastrointestinal disorders		
Common	Nausea	3 (7)
	Vomiting	2 (5)
	Upper abdominal pain	1 (2)
	Lip pain	1 (2)
Skin and subcutaneous tissue disorders		
Common	Rash	1 (2)
	Swelling of face	1 (2)
Injury, poisoning and procedural complications		
Common	Endotracheal intubation complication	1 (2)
	Wound dehiscence	1 (2)

[a] *Includes verbatim terms suture irritation and suture reaction*

[b] *Includes verbatim term subretinal precipitate*

[c] *Includes verbatim terms epiretinal membrane and macular pucker*

[d] *Includes verbatim term macular thinning*

[e] *Includes verbatim term foveal dehiscence*

[f] *Includes verbatim terms foveal thinning and loss of foveal function*

[g] The adverse effect retinal tear was assigned the frequency category "common" in line with CIOMS III as the unrounded frequency was ≥1/100 to <1/10 (9.75%; 4/41).

Description of selected adverse effects

Immunogenicity

At all doses of Luxturna evaluated in Studies 101 and 301 immune reactions were mild in severity and extra-ocular exposure was limited. In Study 101 the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 301 the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No patient had a clinically significant cytotoxic T-cell response to the adeno-associated virus serotype 2 [AAV2] vector or the retinal pigment epithelium-specific 65 kDa protein [RPE65].

Patients received systemic corticosteroids before and after subretinal injection of Luxturna in each eye. The corticosteroids may have decreased the potential immune reaction to the vector capsid [AAV2] or transgene product [RPE65].

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal EIViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

There is no known clinical experience with overdose of voretigene neparvovec.

Treatment

In case of overdose, symptomatic and supportive treatment is recommended.

Properties/Actions

ATC code:

S01XA27

Mechanism of action

Luxturna was developed to deliver a normal copy of the gene encoding the human retinal pigment epithelium-specific 65 kilodalton protein (RPE65) to cells of the retina in persons with reduced or absent levels of biologically active RPE65. RPE65 is produced in the retinal pigment epithelial (RPE) cells and converts all-trans-retinol to 11-cis-retinol, which is subsequently converted to the chromophore, 11-cis-retinal, during the visual (retinoid) cycle. The visual cycle is critical in phototransduction, i.e. the biological conversion of a photon of light into an electrical signal in the retina. Over time, accumulation of toxic intermediates leads to the death of retinal pigment epithelial cells and subsequently to

progressive photoreceptor cell death, resulting in impairment of vision and ultimately complete blindness.

Pharmacodynamics

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

Clinical efficacy

Clinical studies: Study 301

The efficacy of Luxturna in paediatric and adult patients was evaluated in an open-label, two-centre, randomised study (Study 301).

Of the 31 patients (13 male, 18 female) enrolled in the study, 21 were randomised to receive a subretinal injection of Luxturna. DNA tests for the presence of biallelic *RPE65* mutations and mutation types were performed in a US CLIA-certified laboratory using the Sanger sequencing method. The presence of sufficient viable retinal cells (an area of retina within the posterior pole of >100 micron thickness as determined by optical coherence tomography [OCT]) was established for all participants. The mean visual acuity (LogMAR) of the first eye of these patients at baseline was 1.18 (standard error 0.14). One patient was excluded from the study prior to treatment. 10 patients were randomised to the control (non-intervention) group. One patient in the control group withdrew their consent and was therefore excluded from the study. The nine patients who were randomised to the control group crossed over to the intervention group to receive a subretinal injection of Luxturna after one year of observation. The average age of the 31 randomised patients was 15 years (age range 4 to 44 years), including 64% paediatric patients (n=20, aged 4 to 17 years) and 36% adults (n=11). Bilateral subretinal injections of Luxturna were carried out one after the other in two separate surgical procedures with an interval of 6 to 18 days between the injections.

The primary endpoint of the phase 3 study measured the mean change from baseline to one year in both eyes between the intervention and control groups using multi-luminance mobility testing (MLMT).

The MLMT was designed to measure changes in functional vision, specifically the ability of a patient to complete a course accurately and at a reasonable pace at different levels of environmental illumination. This ability depends on the patient'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.

The MLMT was assessed using both eyes (binocular vision) and each eye separately at one or more of seven levels of brightness, ranging from 400 lux (corresponding, for example, to a brightly lit office) to 1 lux (corresponding, for example, to a moonless summer night). Each level of brightness was assigned a score ranging from 0 to 6. A higher score indicated that a patient was able to pass the MLMT

at a lower brightness. The MLMT of each patient was videoed and assessed by independent graders using a defined combination of speed and accuracy values. The MLMT score was determined by the lowest brightness level at which the patient passed the MLMT. The MLMT score change was defined as the difference between the score at baseline and after one year. A positive score change from baseline to year 1 indicated that the patient was able to complete the MLMT at a lower brightness level, with a lux score of 6 reflecting 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 eye treated and visual acuity (VA) testing.
Table 2 summarises the average MLMT score change from baseline to year 1 in the Luxturna treatment group compared to the control group. At baseline patients passed the mobility test at levels of illumination of between 4 and 400 lux.

Table 2 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 both eyes	1.6 (0.72; 2.41)	0.001
Using only the first eye treated	1.7 (0.89; 2.52)	0.001
Using only the second eye treated	2.0 (1.14; 2.85)	<0.001

The analysis of bilateral MLMT change score for the intention-to-treat (ITT) population showed a statistically significant treatment effect, with a mean group difference (95% confidence interval [CI]) of 1.6 (0.72, 2.41; p=0.001).

The monocular MLMT score change significantly improved in the treatment group and was similar to the binocular MLMT results (see Table 2).

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

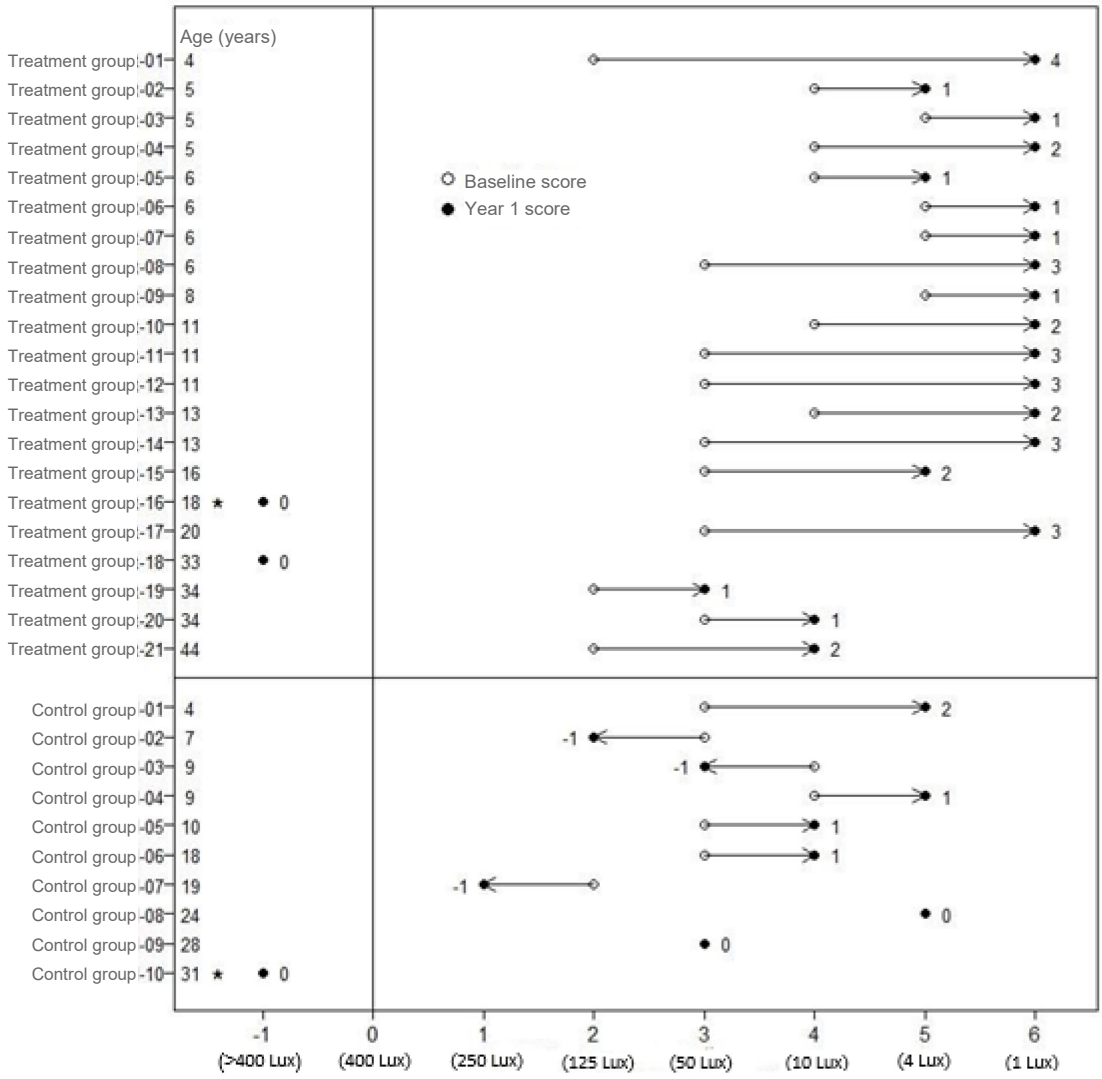
It must be borne in mind that 8 patients (38%) in the Luxturna group had a change in MLMT score of one, while 3 patients from the control group (30%) also had an improvement in MLMT score of one. Therefore, the improvement of 1 in MLMT score could also be interpretable as a day-dependent fluctuation.

Table 3 Magnitude of MLMT score change using both eyes at year 1

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 1 shows MLMT results of individual patients using both eyes at baseline and at year 1.

Figure 1 Binocular MLMT score at baseline and one year for individual patients

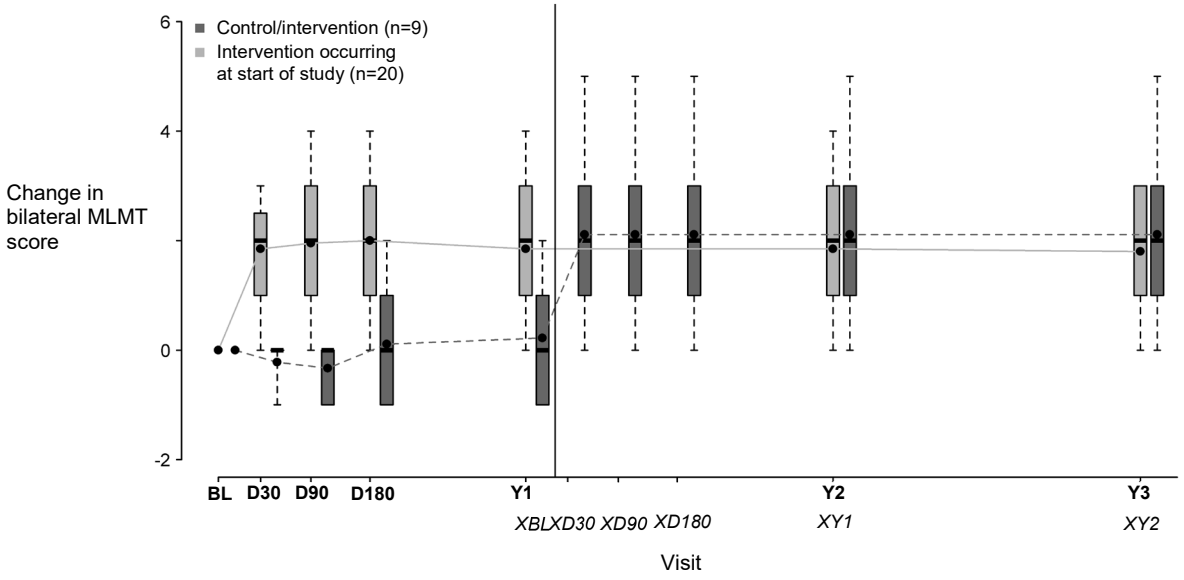


*Note on Figure 1: *Patients who were excluded from the study or discontinued it. The open circles are the baseline scores. The closed circles are the scores at year 1. The numbers next to the closed circle correspond to the score changes at year 1. The horizontal lines with arrows represent the magnitude of the change and its direction.*

Arrows pointing towards the right represent improvement. The top section shows the results of the 21 patients in the treatment group. The bottom section shows the results of the 10 patients in the control group. Patients in each group are chronologically ordered by age, with the youngest patient at the top and the oldest at the bottom.

Figure 2 shows the effect of the medicinal product over the 3-year period in the voretigene neparvovec treatment group as well as the effect in the control group after crossing over to the intervention group and receiving subretinal injection of voretigene neparvovec. Significant differences in binocular MLMT results were determined for the voretigene neparvovec treatment group at day 30, which were able to be maintained over the remaining follow-up visits throughout the three-year period, compared the control group, in which there was no change. However, after crossing over to the intervention group and receiving subretinal injection of voretigene neparvovec, the patients in the control group showed a similar response to voretigene neparvovec to the patients in the voretigene neparvovec treatment group.

Figure 2 Change in MLMT score using both eyes vs time before/after exposure to voretigene neparvovec



Note on Figure 2: Each box represents the middle 50% of distribution of MLMT score changes. The vertical dotted lines represent the 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 changes over visits for the control group, including the five visits during the first year without voretigene neparvovec treatment. The control group was administered voretigene neparvovec after one 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 group after crossover to intervention group;

XY1; XY2: one and two years after start of study for control group after crossover to intervention group.

Full-field light sensitivity threshold (FST) testing is a global measure of retinal sensitivity to light, whereby Log10(cd.s/m^2) values indicate better sensitivity the more negative they are. Results of full-field light sensitivity threshold (FST) testing using white light in the first study year [Log10(cd.s/m^2)] are listed in Table 4 below.

Table 4 Full-field light sensitivity threshold testing

Full-field light sensitivity threshold testing – with first treated eye (ITT)			
	Intervention, N=21		
	Baseline	**Year 1**	**Change**
N	20	20	19
Mean (standard error)	-1.23 (0.10)	-3.44 (0.30)	-2.21 (0.30)
	Control, N=10		
N	9	9	9
Mean (standard error)	-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 threshold testing – with second treated eye (ITT)			
	Intervention, N=21		
	Baseline	**Year 1**	**Change**
N	20	20	19
Mean (standard error)	-1.35 (0.09)	-3.28 (0.29)	-1.93 (0.31)
	Control, N=10		
N	9	9	9
Mean (standard error)	-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 threshold testing – averaged across both eyes (ITT) Difference (95% CI) (intervention-control): -2.11 (-3.19; -1.04), p<0.001			

After crossing over to the intervention group and receiving voretigene neparvovec at year 1 patients in the control group showed a similar response to voretigene neparvovec to patients in the original intervention group. In both treatment groups the improvement in FST results following vector administration was greater than 2 log units, corresponding to more than a 100-fold improvement in light sensitivity. The improvement in full-field light sensitivity was maintained for up to 3 years after administration of voretigene neparvovec.

A supportive analysis showed that the linear relationships between the experimental MLMT scores and usual clinical FST in this study were generally good to strong, indicating that patients with improvement in mobility testing at year 1 tended to have lower (i.e. better) FST results at year 1.

One year after exposure to voretigene neparvovec the mean change from baseline in visual acuity for both eyes using the Holladay scale was -0.16 LogMAR for the intervention group and 0.01 LogMAR for the untreated control group. This reflected a mean improvement of 8 letters on the ETDRS chart for patients in the intervention group compared to a mean 0.5-letter loss for patients in the control group. This difference between groups was not statistically significant.

Pharmacokinetics

It is assumed that voretigene neparvovec is taken up by cells through heparan sulphate proteoglycan receptors and degraded by endogenous proteins and DNA degradation pathways.

Absorption

Not applicable.

Distribution

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.

Preclinical data

Biodistribution of voretigene neparvovec was evaluated at three months following subretinal administration in non-human primates. The highest concentrations of vector DNA sequences were detected in intraocular fluids (anterior chamber fluid and vitreous) of vector-injected eyes. Low concentrations 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. In one animal administered Luxturna at 7.5×10^{11} vg (5 times the recommended per-eye dose) vector DNA sequences were detected in the colon, duodenum and trachea. Vector DNA sequences were not found in the gonads.

Clinical data

Luxturna vector shedding and biodistribution were investigated in a study measuring Luxturna DNA in lacrimal fluid from both eyes, serum and whole blood of patients in Study 301. In summary, Luxturna vector was detected transiently and at low levels in lacrimal fluid from the injected eye in 45% of patients in Study 301 and occasionally (7%) from the uninjected eye until day 3 post injection.

In 13/29 (45%) patients receiving bilateral administration Luxturna vector DNA sequences were detected in tear samples. Peak levels of vector DNA were detected in the tear samples on day 1 post injection; thereafter, no vector DNA was detected in the majority of the patients (8 of 13). In three patients (10%) vector DNA was detected in tear samples until day 3 post injection and in two patients (7%) vector DNA was detected in tear samples for around two weeks post injection. In another two patients (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 following each injection up to day 3 in 3/29 (10%) patients, including two patients with positive results in tear samples.

Overall, transient and low levels of vector DNA were detected in lacrimal fluid and occasionally in serum samples in 14/29 (48%) of patients 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 processes are not expected to influence the clinical efficacy or safety of the medicinal product. Therefore, no dose adjustment is necessary in patients with hepatic or renal impairment.

Preclinical data

Bilateral, simultaneous subretinal administration of voretigene neparvovec was well tolerated at doses up to 8.25 x 10^{10} vg per eye in dogs with a naturally occurring RPE-65 mutation and at a dosage of 7.5 x 10^{11} vg (5 times higher than the recommended human dose) 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 of 1.5 x 10^{11} vg per eye. In addition, dogs with the RPE-65 mutation displayed improved visual behaviour and pupillary responses.

Ocular histopathology of dogs and non-human primates whose eyes were exposed to voretigene neparvovec showed only mild changes, which were mostly related to the process of healing from surgery. In an earlier toxicology study a similar AAV2 vector administered subretinally in dogs at a dose of 10 times the recommended dose resulted histologically in focal retinal toxicity and infiltration with inflammatory cells in regions exposed to the vector. Other findings from voretigene neparvovec preclinical 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.

Mutagenicity and carcinogenicity

No animal studies have been conducted to evaluate the effects of voretigene neparvovec on carcinogenicity or mutagenicity.

Other information

Incompatibilities

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

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.
Unopened frozen vials: 24 months.

Shelf life after opening

Luxturna does not contain any preservatives.

Luxturna should be used immediately following thaw of the vials.

If necessary, it may be stored at room temperature (15 to 25˚C) for up to 4 hours prior to administration.

Vials must not be re-frozen.

Special precautions for storage

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

Keep out of the reach of children.

Instructions for use and handling

For subretinal use only.

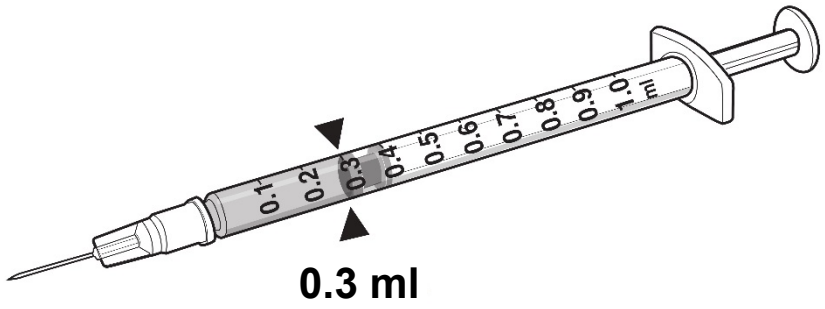
Preparation of Luxturna must take place within 4 hours before administration using sterile technique and under aseptic conditions in a class II vertical laminar flow biological safety cabinet (BSC). Below you will find the list of items required for dilution of the concentrate and preparation of the injection syringe:

- One single-dose vial of Luxturna
- Two vials of solvent
- One sterile 3 ml syringe
- One sterile needle (20G x 25 mm)
- Three sterile biocompatible 1 ml syringes
- Three sterile needles (27G x 13 mm)
- Two sterile syringe caps
- One sterile empty 10 ml glass vial
- One sterile drape
- One sterile plastic bag
- Two sterile labels for injection needles
- One sterile plain label
- One sterile skin marker

Dilution of Luxturna

1. Thaw one single-dose vial of Luxturna and two vials of solvent at room temperature.
2. Gently invert the thawed solvent vials 5 times to mix the contents.
3. Inspect the solvent vials. If particulates, cloudiness or discolouration are visible, do not use the vial(s); in this case (a) new vial(s) of solvent must be used.
4. Lay out one sterile 3 ml syringe, one sterile 20G x 25 mm needle and one sterile empty 10 ml glass vial.
5. Using the 3 ml syringe and 20G x 25 mm needle, transfer 2.7 ml of solvent into the 10 ml glass vial. Dispose of the needle and syringe in an appropriate container.
6. Gently invert the thawed Luxturna single-dose vial 5 times to mix the contents.
7. Inspect the Luxturna single-dose vial. If particulates, cloudiness or discolouration are visible, do not use the vial; in this case a new Luxturna single-dose vial must be used.
8. Lay out one sterile 1 ml syringe and one sterile 27G x 13 mm needle. Draw 0.3 ml of Luxturna into a sterile 1 ml syringe using a sterile 27G x 13 mm needle (Figure 5).

Figure 5 Syringe with 0.3 ml Luxturna



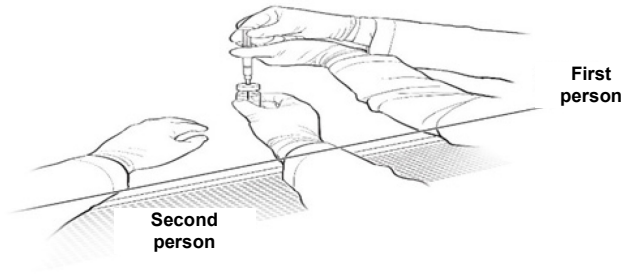
9. To dilute, transfer 0.3 ml of Luxturna into the 10 ml glass vial containing 2.7 ml of solvent from step 5. Gently invert the glass vial approximately 5 times to mix the contents.
10. Using the sterile plain label and sterile skin marker, label the 10 ml glass vial containing the diluted Luxturna as follows: “Diluted Luxturna”.
11. Remove all items from the biological safety cabinet except the glass vial labelled “Diluted Luxturna” and the sterile skin marker.
12. Re-sanitise the safety cabinet prior to the next steps and place the glass vial and the sterile skin marker on the left side of the safety cabinet.

Preparation of Luxturna for injection

To keep the syringes sterile, two people are required to transfer the contents of the 10 ml glass vial labelled “Diluted Luxturna” into each of the two sterile 1 ml syringes.

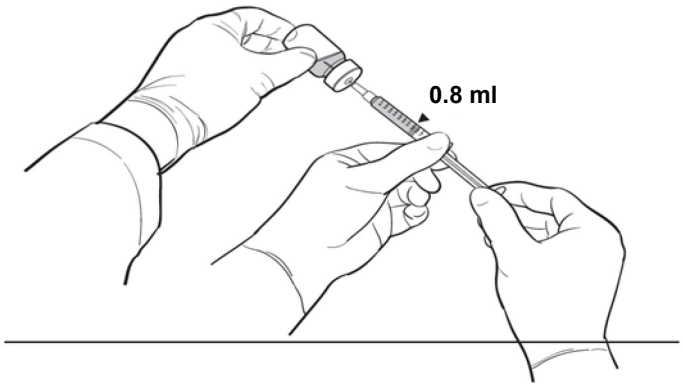
13. Lay out a sterile drape, a sterile plastic bag and two sterile labels in the safety cabinet.
14. Place the sterile drape near the first person on the right side of the disinfected surface of the safety cabinet, away from the diluted Luxturna.
15. The second person unwraps two 1 ml syringes, two 27G x 13 mm needles and two syringe caps in the safety cabinet, ensuring that the first person touches only sterile surfaces while transferring the items onto the sterile drape.
16. The second person puts on a new pair of sterile gloves and stands or sits to the left of the first person. The second person holds the 10 ml glass vial containing the diluted Luxturna (Figure 6).

Figure 6 First position during preparation of Luxturna syringes



17. The first person withdraws 0.8 ml of diluted Luxturna into a sterile 1 ml syringe using a sterile 27G x 13 mm needle while the second person holds the 10 ml glass vial. After the insertion of the needle the second person turns the 10 ml glass vial, enabling the first person to withdraw 0.8 ml without touching the 10 ml glass vial (Figure 7).

Figure 7 Second position during preparation of Luxturna syringes



18. The first person 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 injection syringe.
19. The first person repeats steps 17 and 18 to prepare a total of two injection syringes. The first syringe is labelled “Diluted Luxturna” and the second syringe “Backup diluted Luxturna” using the

sterile skin marker. The second syringe serves as a backup for the surgeon performing the subretinal injection. The backup syringe must be discarded after surgery if not used.

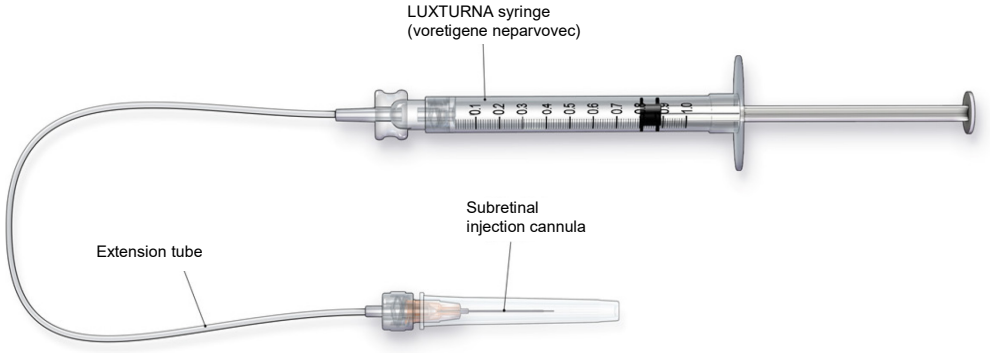
20. Inspect both syringes. If particulates, cloudiness or discolouration are visible, do not use the syringe.
21. Place the syringes into the sterile plastic bag after visual inspection and seal the bag.
22. Place the sterile plastic bag with the syringes containing diluted Luxturna into an appropriate secondary container (e.g. hard plastic cooler) and transport it to the operating room at room temperature.

Method of administration

Luxturna should be administered in the operating room under controlled aseptic conditions by a surgeon experienced in performing intraocular surgery. In addition to the syringe containing the diluted Luxturna the following aids are required for administration (Figure 8):

- Biocompatible subretinal injection cannula with a polyamide micro tip with an inner diameter of 41 gauge.
- Biocompatible extension tube made of polyvinyl chloride no longer than 15.2 cm in length and with an inner diameter no greater than 1.4 mm.

Figure 8 Injection apparatus assembly



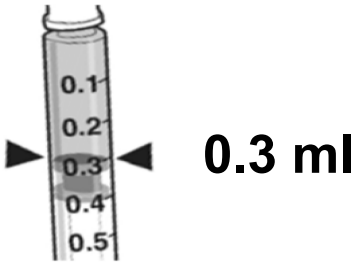
Proceed as follows for the subretinal injection:

1. After confirming the availability of Luxturna, dilate the eye and administer adequate anaesthesia to the patient.
2. Administer a topical broad-spectrum microbicide to the conjunctiva, cornea and eyelids prior to surgery.
3. Inspect Luxturna prior to administration. If particulates, cloudiness or discolouration are visible, do not use the medicinal 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 medicinal product slowly through the extension tube and the subretinal injection cannula to remove any air bubbles.

5. Check the injectable volume of medicinal product in the syringe by aligning the plunger tip with the 0.3 ml mark (Figure 9).

Figure 9 Volume of Luxturna for injection



6. After vitrectomy is completed, the intended site of administration is determined. The subretinal injection cannula can be introduced via pars plana (Figure 10).
7. Under direct visualisation the tip of the subretinal injection cannula is placed on the retinal surface. The recommended site of injection is located along the superior vascular arcade, at least 2 mm distal to the centre of the fovea centralis (Figure 11). Direct contact with the retinal vasculature or with areas of pathologic features such as dense atrophy or intraretinal pigment migration must be avoided. A small amount of the medicinal product is slowly injected until an initial subretinal bleb is visible. The remaining volume is then slowly injected until the total 0.3 ml is delivered.

Figure 10 Subretinal injection cannula introduced via pars plana

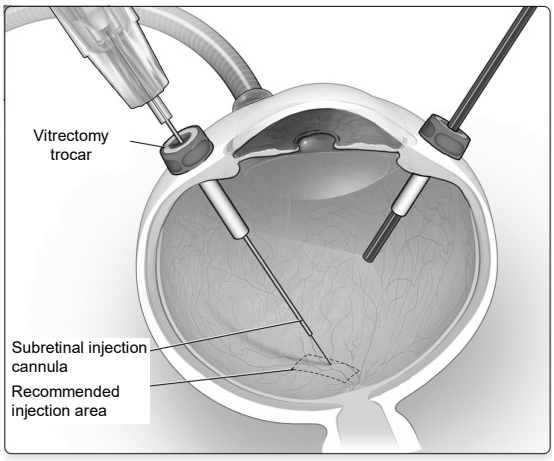
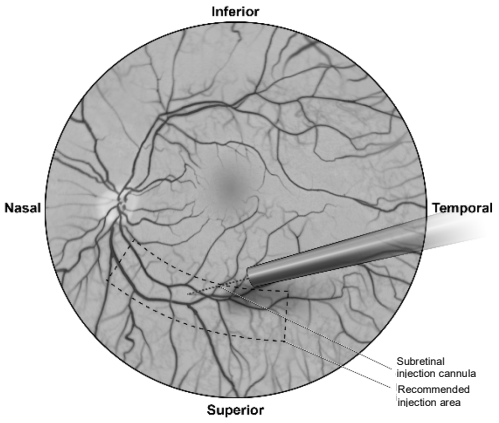


Figure 11 Tip of the subretinal injection cannula within the recommended injection area (surgeon's point of view)



8. After the injection is complete, the subretinal injection cannula is removed from the eye.

9. After injection any unused medicinal product must be discarded. The backup syringe must be disposed of according to local biosafety guidelines applicable to the handling and disposal of the medicinal product.
10. Perform a fluid-gas exchange, carefully avoiding fluid drainage near the retinotomy site created for the subretinal injection.
11. The patient should assume a supine position immediately after surgery.
12. The patient should remain in this lying position as much as possible, including after discharge, for up to 24 hours at the physician's discretion.

Accidental exposure

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

- Personal protective equipment (including laboratory coat, safety glasses and gloves) should be worn while preparing or administering voretigene neparvovec.
- Accidental exposure to voretigene neparvovec, including contact with skin, eyes and mucous membranes, is to be avoided. Any exposed wounds must be covered before handling.
- Any spilled fluid containing voretigene neparvovec must be treated with a virucidal agent such as 1% sodium hypochlorite and blotted 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 regulations.

Measures to be taken in the event of accidental exposure:

- In the event of an accidental occupational exposure to the medicinal product (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.

Special precautions for disposal

This medicinal product contains genetically modified organisms. Unused medicinal product must be disposed of in compliance with the institutional guidelines for genetically modified organisms or biohazardous waste.

Swissmedic number

67371

Pack sizes

0.5 ml extractable volume of concentrate in 2 ml cyclic olefin polymer vial with a chlorobutyl rubber stopper sealed with an aluminium flip-off seal.
1.7 ml extractable volume of solvent in 2 ml cyclic olefin polymer vial with a chlorobutyl rubber stopper sealed with an aluminium flip-off seal.
Each foil pouch includes a carton containing one vial of concentrate and two vials of solvent (for single use only). [A]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

Information last revised

February 2020