Regulatory Affairs

Voretigene Neparvovec

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*AAV2-hRPE65V2* *Voretigene Neparvovec*
Product(s) concerned (brand name(s)):	*Luxturna*
Document status:	*Final*
Version number of the RMP Public Summary:	*2.0*
Date of final sign off of the RMP Public Summary	*07.03.2022*

Template version 2.0 Feb 2022

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of “Luxturna” is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of “Luxturna” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Luxturna”.

Table of contents

This is a summary of the risk management plan (RMP) for voretigene neparvovec. The RMP details important risks of Luxturna, how these risks can be minimized, and how more information will be obtained about Luxturna's risks and uncertainties (missing information). Luxturna's summary of product characteristics (FI) and its package leaflet give essential information to healthcare professionals and patients on how Luxturna should be used.
This summary of the RMP for Luxturna should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Luxturna's RMP.

I. The medicine and what it is used for

Luxturna is authorised 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. (see Information for Professionals for the full indication). It contains voretigene neparvovec as the active substance and it is given by subretinal injection.
Biallelic mutations in the RPE65 gene lead to inherited disease causing ongoing deterioration of the retina. The gene mutation leads to decreased or lack of the activity of the enzyme retinoid isomerohydrolase which is encoded by RPE65 gene and eventually leads to the accumulation of toxic precursors and reduced functioning of the cells in the retina. The pattern of inheritance is autosomal recessive i.e. both parents are carriers or have one defective copy of the gene. Leber congenital amaurosis (LCA) is estimated to affect ~1/81,000 of individuals. 8-16% of these patients are identified as having mutations in the RPE65 gene. The condition can affect both children and adults, both male and female and the first signs of the condition can appear as soon as 2-3 months of age. The condition is usually diagnosed within the first few months of life and leads to severe visual impairment, abnormal eye movements (nystagmus) and will progress to total blindness.
Some patients with autosomal recessive RPE65 gene mutations may have been diagnosed with retinitis pigmentosa, which has a more variable age of onset and extent of vision loss than LCA. Retinitis pigmentosa (RP) is estimated to affect approximately 1/3,500 to 1/4,000 individuals.
It is estimated that a range of 1 to 3% of all patients with RP have underlying genetic mutations in the RPE65 gene. The condition can affect both children and adults, both male and female. The condition has a more variable age of onset than LCA but similarly leads to severe visual impairment, abnormal eye movements (nystagmus) and will progress to total blindness. There are no other pharmacological treatments approved for RPE65 mutation-associated inherited retinal disease.

Further information about the evaluation of Luxturna's benefits can be found in Luxturna's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/luxturna.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Luxturna, together with measures to minimize such risks and the proposed
studies for learning more about Luxturna's risks, are outlined below.
Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and Information for Professionals addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.
In the case of Luxturna, these measures are supplemented with additional risk minimization
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
If important information that may affect the safe use of Luxturna is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Luxturna are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Luxturna. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 - List of important risks and missing information

Important identified risks	Increased intraocular pressure Retinal tear Macular disorders Cataracts Intraocular inflammation and/or infection related to the procedure Retinal detachment
Important potential risks	Tumorigenicity Host immune response Third party transmission Vision loss due to progressive chorioretinal atrophy
Missing information	Long-term efficacy (>4 years) Use in pregnancy and lactation Use in children <3 years of age Long-term safety (>9 years)

II B: Summary of important risks

Table 2 Important identified risk: increased intraocular pressure

Evidence for linking the risk to the medicine	These events have been seen in the clinical trials; Eight of the 41 (20%) subjects in the clinical program reported an event of intraocular pressure (IOP) increased. Overall, 10 (12%) of the 81 injected eyes had an event of intraocular pressure increased. One event was in an uninjected eye. Most were considered related to the administration of the product. In the literature increased IOP is a documented risk with the surgical procedure. Studies on eye surgery (vitrectomy) showed the incidence of increased IOP after surgery to range from 20-60%. In a prospective study in this type of eye surgery (pars plana vitrectomy), approximately 60% of patients had an acute IOP rise within 48 hours after surgery with no significant difference between IOP before and much later after the operation. In a study

	looking at data retrospectively on 111 eyes, after an average follow up of 49 months, there was no long term increase in IOP following eye surgery (pars plana vitrectomy).
Risk factors and risk groups	Presence or history of glaucoma or elevated intraocular pressure. Incorrect administration technique. Raised IOP has also been associated with prolonged topical as well as systemic steroid use.
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.4 and 4.8 • PL section 2 and 4 Recommendation for patients to avoid air travel or other travel to high elevations until the air bubble formed as a result of Luxturna administration has dissipated from the eye, which should be verified by an ophthalmic examination in Information for Professionals section 4.4 and PL section 2 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 3 Important identified risk: retinal tear

Evidence for linking the risk to the medicine	These events have been seen in the clinical trials and were considered related to the administration procedure. Four of 81 (5%) eyes in 4 of 41 (10%) subjects administered voretigene neparvovec in the clinical program had a retinal tear, all of which were repaired during the administration procedure. In the literature, it is documented that retinal tears are a significant complication of eye surgery (vitrectomy) with an incidence of about 5%-15%, with retinal detachment after the surgery occurring in 2-4% of affected eyes.
Risk factors and risk groups	Risk factors include myopia, lattice degeneration, previous eye surgery, and trauma. Incorrect administration procedure technique.
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.4 and 4.8 • PL section 2 and 4 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

	• A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 4 Important identified risk: macular disorders

Evidence for linking the risk to the medicine	These events have been seen in clinical trials. Overall, 10 (12%) of 81 eyes administered Luxturna in 7 (17%) of 41 subjects in the clinical program reported events grouped as macular disorders (mapped to PT Eye disorder [foveal dehiscence], Macular hole, Macular degeneration [macular thinning], Maculopathy, and Retinal disorder [foveal thinning and loss of foveal function]). All events were considered related to the procedure and none were considered related to the product. From the literature a study of 45 patients undergoing eye surgery (pars plana vitrectomy) for fibrous covering of the macula due to unknown cause (idiopathic retinal membrane) one patient developed macular hole 6 months post-operatively. Wrinkling on the surface of the retina after vitrectomy for retinal detachment has been reported in 9-13% of eyes. Studies with subretinal administration of a similar viral vector, one group reported a measured thinning of the central macula after delivery of the vector, including 6 of 12 subjects with sustained reduction in macular thickness, through the last assessment at 24 or 36 months. Another group reported two out of 15 subjects with notable examples of foveal thinning in the short-term. Long-term follow-up in one of these two subjects showed that foveal thinning was still present at 24 months post subretinal administration. A third group reported minimal thinning observed within the first few months following treatment and remained stable throughout follow-up at 1 or more than 2 years.
Risk factors and risk groups	Risks include underlying retinal disorder, aging and vitreomacular traction. Incorrect administration procedure technique.
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.4 and 4.8 Advice in Information for Professionals section 4.4 on where Luxturna should not beadministered • PL section 2 and 4 Patients advised regarding which symptoms they should contact the doctor for in PL section 2 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 5 Important identified risk: cataract

Evidence for linking the risk to the medicine	These events have been seen in clinical trials. Cataract was reported in 21 (26%) of 81 eyes in 13 (32%) of 41 subjects in the clinical program. Of these, 18 events in 18 eyes were assessed as related to the subretinal administration procedure. Patients with hereditary retinal degeneration have a higher incidence of cataract formation and at a younger age. In a study describing the natural history of retinal degenerative disease in individuals with autosomal recessive mutations in the RPE65 gene, cataracts or other cloudiness of the lens were seen in at least one eye in 14 (20.0%) subjects: 11 (78.5%) had bilateral lens abnormalities, 2 subjects had lens abnormalities in only the right eye and one subject had a lens abnormality in only the left eye. The average age of subjects at the time of first lens abnormality was 26 years of age. After vitrectomy surgery, after 6 months, progression of clouding of the lens (nuclear sclerotic cataract progression) was seen in 60/74 (81%) of eyes compared to 13/74 (18%) with no surgery, and 100% of eyes had progression of cataract after 2 years compared to 8% of eyes with no surgery. In a retrospective review of eyes post vitrectomy surgery for macular fibrosis, 80/100 eyes developed cataract leading to significant problems with vision or had undergone cataract extraction compared to 24/100 in the group without surgery.
Risk factors and risk groups	Risks include aging, trauma, and vitrectomy. Also associated with inherited retinal disease.
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.8 • PL section 2 and 4 Patient advised regarding which symptoms they should contact the doctor for in PL Section 2 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 6 Important identified risk: intraocular inflammation and/or infection related to the procedure

Evidence for linking the risk to the medicine	These events have been seen in the clinical trials. Events grouped as eye inflammation and/or infection (mapped to PT Eye inflammation) was reported in 5 of 81 (6%) eyes in 3 of 41 (7%) subjects in the clinical program, including one event in one eye (1/81, 1%) of intraocular infection (culture-positive endophthalmitis). All events were considered related to the procedure. In the literature, it is noted that infection inside the eye (endophthalmitis) can occur after eye surgery (vitrectomy) for any cause, but it is rare. The incidence of endophthalmitis post pars plana vitrectomy has been reported to be

	between 0.03% and 0.07%. The rate of infection inside the eye after surgery for lens implantation was 0.2%.
Risk factors and risk groups	Risks include incorrect administration procedure technique.
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.2, 4.3, 4.4 and 4.8 • PL section 2 and 4 Guidance regarding aseptic technique and use of topical microbicide in Information for Professionals section 4.2. States what symptoms the patients need to be informed to report without delay in Information for Professionals section 4.4 and PL section 2. Avoidance of swimming in Information for Professionals section 4.4 and PL section 2. • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 7 Important identified risk: retinal detachment

Evidence for linking the risk to the medicine	Two (2.5%) of 81 eyes in two (5%) of 41 subjects administered voretigene neparvovec in the clinical program had a retinal detachment. Both events (one per subject) were assessed as related to the subretinal administration procedure. In the literature, in a study of 645 eyes undergoing vitrectomy, retinal tears occurred in 15.2% of eyes intraoperatively, and resulting postoperative retinal detachment occurred 1.7% of eyes at a median of 7.5 weeks (range 3-40 weeks). Another study reported postoperative retinal detachment in 4% of 173 eyes undergoing vitrectomy for fibrous membrane removal, with a mean time to presentation at 3.75 months after vitrectomy.
Risk factors and risk groups	These events are usually spontaneous and cannot be predicted. Myopia, lattice degeneration, pars plana vitrectomy, trauma, and family history are risk factors for retinal detachment.
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.2 and 4.4 • PL section 2 and 4 States what symptoms the patients need to be informed to report without delay in Information for Professionals section 4.4 and PL section 2 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product • Patient card

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 8 Important potential risk: tumorigenicity

Evidence for linking the risk to the medicine	This is an advanced therapeutic medicinal product (ATMP)-specific risk consideration. Under the post-marketing set-up, no cases of tumor formation have been reported.
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 9 Important potential risk: host immune response

Evidence for linking the risk to the medicine	Evidence from the literature. This is also an ATMP specific risk consideration.
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.2 • PL section 3 The immunomodulatory regime to be used is stated in the Information for Professionals section 4.2 and referenced PL section 3. • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 10 Important potential risk: third party transmission

Evidence for linking the risk to the medicine	ATMP specific risk consideration – Environmental Risk Assessment There were no instances of third party transmission noted during the clinical development.

	During the post-marketing set-up, no cases of suspected or confirmed third party transmission have been reported.
Risk factors and risk groups	Healthcare workers, caregivers or other close contacts of the treated individual (partners and family members) including pregnant women and immunosuppressed individuals are particularly at risk of third party transmission.
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.4, 5.2 and 6.6 Advice on how to handle waste material from dressings, tears and nasal secretions and on personal protective equipment in section 4.4. An exclusion from donation of blood, organs, tissues, and cells for transplantation is included. Advice on managing accidental exposure is in section 6.6. • PL section 2 PL section 2 provides advice on personal protective equipment and disposal of dressings and waste materials. An exclusion from donation of blood, organs, tissues, and cells for transplantation is included. • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) See section II.C of this summary for an overview of the post-authorization development plan.

Table 11 Important potential risk: Vision loss due to progressive chorioretinal atrophy

Evidence for linking the risk to the medicine	Cases of progressive chorioretinal atrophy have been described from post marketing experience and published literature. Events were temporally related to treatment and occurred in the estimated treated area of the bleb site. None of the post-injection retinal atrophies reported significant visual functional impairment associated with the event. It is unknown whether retinal atrophy might potentially extend to the fovea.
Risk factors and risk groups	No risk factors or risk groups have been confirmed.
Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.8 • PL section 4 • Prescription only product Additional risk minimization measures: • Distribution through treatment centers who have received mandatory training on use of product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) See section II.C of this summary for an overview of the post-authorization development plan.

Table 12 Missing information: long-term efficacy (> 4 years)

Risk minimization measures	Routine risk minimization measures:

	• Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 13 Missing information: use in pregnancy and lactation

Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.6 • PL section 2 • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

Table 14 Missing information: use in children < 3 years of age

Risk minimization measures	Routine risk minimization measures: • Information for Professionals section 4.2 • PL section 2 • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401) See section II.C of this summary for an overview of the post-authorization development plan.

Table 15 Missing information: long-term safety (> 9 years)

Risk minimization measures	Routine risk minimization measures: • Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01) See section II.C of this summary for an overview of the post-authorization development plan.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

Table 16 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study
A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe and other countries (ex-US) (CLTW888A12401)	The objective of this registry-based study is to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
Long-term follow-up study for participants in the clinical program conducted in the US (LTFU-01)	This is a long-term safety and efficacy follow-up study of trial participants who received Luxturna in the clinical program.

II.C.2. Other studies in post-authorization development plan

There are no studies required for Luxturna under this category.