Part VI: Summary of the risk management plan

Summary of risk management plan for Luxturna (Voretigene neparvovec)

This is a summary of the risk management plan (RMP) for Luxturna. The RMP details important risks of Luxturna, how these risks can be minimised, and how more information will be obtained about Luxturna's risks and uncertainties (missing information).

Luxturna's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Luxturna should be used. As Luxturna is used for a condition that is rare in the population the approval for the medicine will be approved as an orphan drug due to this.

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 SmPC for the full indication). It contains voretigene naparvovec 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 ie both parents are carriers or have one defective copy of the gene. Leber congenital amaurosis 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 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 minimise or further characterise the risks

Important risks of Luxturna, together with measures to minimise such risks and the proposed studies for learning more about Luxturna's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Luxturna, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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 minimise 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);

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
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

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 programme reported an event of intraocular pressure (IOP) increased. Overall, 10 (8%) 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 procedure technique. Raised IOP has also been associated with topical steroid use (Thomas, 1988).
Risk minimisation measures	Routine risk minimisation measures: SmPC 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 has dissipated from the eye, which should be verified by an ophthalmic examination in SmPC section 4.4 and PL section 2 Prescription only product Additional risk minimisation measures Distribution through treatment centres 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

	Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

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 programme 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, intraocular surgery, trauma, and family history. Incorrect administration procedure technique.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2 and 4 Prescription only product Additional risk minimisation measures Distribution through treatment centres 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 Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Macular disorders	
Evidence for linking the risk to the medicine	These events have been seen in clinical trials. Overall, 9 of 81 (11%) eyes administered Luxturna in 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 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 six 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 aging and vitreomacular traction. Incorrect administration procedure technique.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2 and 4 Advice on where to administer not to administer Luxturna in SmPC section 4.4

	Patient advised regarding which symptoms they should contact the doctor for in PL section 2 Prescription only product Additional risk minimisation measures Distribution through treatment centres 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 Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Cataract	
Evidence for linking the risk to the medicine	These events have been seen in clinical trials. Cataract was reported in 16 of 81 (20%) eyes in nine of 41 (22%) subjects in the clinical programme. Not all events were considered related to the 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 the right eye of 13 (18.6%) subjects, the left eye in 12 (17.1%) subjects and in both eyes in 14 (20.0%) subjects. 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, vitrectomy. Also associated with inherited retinal disease. Incorrect administration procedure technique.
Risk minimisation measures	Routine risk minimisation measures: SmPC 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 minimisation measures Distribution through treatment centres 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 Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.
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. Eye inflammation was reported in 5 of 81 (6%) eyes in 3 of 41 (7%) subjects in the clinical programme, 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 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 minimisation measures	Routine risk minimisation measures: SmPC 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 SmPC section 4.2. States what symptoms the patients need to be informed to report without delay in section 4.4 and PL section 2 Avoidance of swimming in SmPC section 4.4 and PL section 2. Prescription only product Additional risk minimisation measures Distribution through treatment centres 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 Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Retinal detachment	
Evidence for linking the risk to the medicine	One of 81 (1%) eyes in 1 of 41 (2%) subjects administered voretigene neparvovec in the clinical programme had a retinal detachment. The retinal detachment was reported 4 years after the administration procedure, and was considered related to the

	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 can't be predicted. Myopia, lattice degeneration, intraocular surgery, trauma, and family history are risk factors for retinal detachment. Incorrect administration procedure technique.
Risk minimisation measures	Routine risk minimisation measures: SmPC 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 section 4.4 and PL section 2 Prescription only product Additional risk minimisation measures Distribution through treatment centres 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 Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Tumorigenicity

Evidence for linking the risk to the medicine	This is an advanced therapeutic medicinal product (ATMP)-specific risk consideration.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation 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 Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

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 minimisation measures	Routine risk minimisation measures: SmPC section 4.2. PL section 3 The immunomodulatory regime to be used is stated in the SmPC section 4.2 and referenced PL section 3 Prescription only medicine

Additional pharmacovigilance activities	Additional pharmacovigilance activities: A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Third party transmission	
Evidence for linking the risk to the medicine	ATMP specific risk consideration – Environmental Risk Assessment
Risk factors and risk groups	Healthcare workers involved in the preparation and administration of Luxturna Healthcare workers or others involved in caring for the patient after administration, which may include those performing washing affected areas or changing dressings. Close contacts of the treated individual (partners and family members)
Risk minimisation measures	Routine risk minimisation measures: SmPC 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 what to do if there is accidental exposure in section 6.6. 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 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term efficacy (>4 years)	
Risk minimisation measures	Routine risk minimisation 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 Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC 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 Long-term follow-up study for participants in the clinical programme

	See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in children < 3 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC 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 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety (>9 years)	
Risk minimisation measures	Routine risk minimisation measures: Prescription only product
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term follow-up study for participants in the clinical programme See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

Study short name: A post-authorization, multicenter, multinational, longitudinal, observational safety registry for patients treated with voretigene neparvovec in Europe

Purpose of the study: This is a single-group, prospective, observational, multi-centre (i.e. in Ocular Gene Therapy Treatment Centres (established by Spark) and inherited retinal dystrophy referral sites) registry designed to collect data on long term safety outcomes in patients treated with the Luxturna.

The study will collect information on patients treated with Luxturna specifically with regards to the safety concerns of increased intraocular pressure, retinal tear, macular disorders, cataract, intraocular inflammation and/or infection related to the procedure, retinal detachment, tumorigenicity, host immune repose, third party transmission, use in pregnancy and lactation, use in patients < 3 years of age and lack of efficacy/decline in efficacy over time. Information on these risks and missing information will be collected and assessed on a regular basis. The study will follow patients for 5 years. A standardised questionnaire will be used to enable collection of information of special interest for review.

A standardized questionnaire will be used that will include a checklist for

- ADRs of special interest
- Local AEs
- General side effects
- Lack of efficacy and/or decline in efficacy over time
- Patients/caregivers assessments

Study short name: Long-term follow-up study for participants in the clinical programme

Purpose of the study: This is a long-term safety and efficacy follow-up study of trial participants who received Luxturna in the clinical programme.

The study will collect long term information on patients who have already received Luxturna as part of the clinical trial programme. The areas that information will be collected on include increased intraocular pressure, retinal tear, macular disorders, cataract, intraocular inflammation and/or infection related to the procedure, retinal detachment, tumorigenicity, host immune repose, use in pregnancy and lactation, long term safety and efficacy. The study is ongoing and it is expected that the last patient will be seen in 2030. The data is reviewed annually.

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

There are no studies under this category.