MINISTRY
OF HEALTH

SECRETARY OF STATE FOR HEALTH

DIRECTORATE GENERAL FOR COMMON NHS
SERVICES PORTFOLIO AND PHARMACY

PHARMACOCLINICAL PROTOCOL FOR THE USE OF VORETIGENE NEPARVOVEC IN THE TREATMENT OF RETINAL DYSTROPHY DUE TO BIALLELIC RPE65 MUTATION IN THE NATIONAL HEALTH SYSTEM

Approved by the Permanent Pharmacy Commission

04/05/2021

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All the experts have made a conflict of interest declaration

TABLE OF CONTENTS

1. INTRODUCTION

Hereditary retinal dystrophies (HRD) are a group of usually degenerative and progressive diseases primarily affecting the photoreceptors, occurring in approximately 1 in 3,000 people[1]. In Spain, a prevalence of 1 per 4,000 inhabitants has been estimated[2], although according to the recently published results for a large Spanish cohort, the prevalence would be 1:7,673[3].

The retinal pigment epithelium-specific 65 kilodalton (kDa) protein (*RPE65*) is localised in retinal pigment epithelium cells and plays a key role in light transduction (biological conversion of a photon of light into an electrical signal within the retina). Mutations in the *RPE65* gene lead to reduced or absent RPE65 activity, blocking the visual cycle and resulting in vision loss. Over time, the accumulation of toxic precursors leads to the death of retinal pigment epithelial cells and subsequently to progressive photoreceptor cell death.

People with HRD associated with the biallelic mutation of the *RPE65* gene show loss of vision, including impairment of visual function parameters such as visual acuity (VA) and visual fields, often during childhood or adolescence. This vision loss eventually progresses to complete blindness[4,5,6,7].

The HRDs caused by bi-allelic mutations in this gene include Leber's congenital amaurosis (LCA) type 2, retinitis pigmentosa 20 (RP20), early onset retinal dystrophy (EOSRD) and early infantile retinal degeneration (SECORD)[8,9].

Leber's congenital amaurosis (ACL) is the earliest and most severe form of all the HRD, as it is responsible for cases of blindness in the first decade of life. Its incidence is 2-3 per 100,000 births, representing 10-18% of cases of childhood blindness and 5% of all HRDs[10,11]. Ten per cent of cases are caused by a defect in the *RPE65* gene[12], although according to different authors cases can be between 6% and 16%[13].

There is currently no curative treatment for this disease. Treatments are aimed at using optical aids as early as possible such as special filters

to increase contrasts, different types of telescopes for distance vision and magnifying lenses for near vision[14].

Retinitis pigmentosa (RP) is a dystrophy of the outer retina caused by the progressive death of photoreceptors through apoptosis, which primarily and initially affects the rods, although as the disease progresses it also affects the cones. The consequent visual deficit is manifested as night blindness, loss of the peripheral visual field and, in most cases, central vision impairment in advanced stages of the disease. It is the most frequent of the HRDs, affecting about 27 out of every 100,000 people in the general population[10]. It is estimated that up to 3% of all patients with RP have biallelic mutations to the *RPE65* gene (RP20)[12,15].

Voretigene neparvovec (Luxturna®) is an orphan gene therapy medicinal product approved for the treatment of adults and children with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells[6,16].

Its administration results in the transduction of retinal pigment epithelial cells with a cDNA encoding the normal human RPE65 protein (gene augmentation therapy), providing the potential to restore the visual cycle.

The efficacy and safety data for voretigene neparvovec are mainly from a pivotal phase III open-label, randomised, controlled trial involving 31 patients with LCA due to RPE65 mutations[17].

One year after administration of voretigene neparvovec, the mean (95% CI) difference in the bilateral multi-luminance mobility test (MLMT) score (the primary study variable) between the treated and control groups (based on the ITT population) was +1.6 (0.72, 2.41), p<0.001

In the full-field light sensitivity test (FST) after one year, the mean difference in score (95% CI) between the intervention and control groups was -2.33 (-3.44-1.22), p<0.001 for the first treated eye and -1.89 (-3.03-0.75), p<0.002 for the second treated eye.

One year after exposure to voretigén neparvovec, an improvement in visual acuity of at least 0.3 LogMAR occurred in 11 (55%) of 20 patients in the first eye and in

4 (20%) of 20 in the second eye in the intervention group; none of the patients in the control group showed such improvement in visual acuity.

2. TREATMENT OBJECTIVE

The goal in treatment with voretigene neparvovec is to restore the function of the pigment epithelium and to stop photoreceptor cell death and vision loss.

3. PATIENT SELECTION CRITERIA[7,12, 16]

Patients who meet **all** the following criteria, which must be adequately documented, are considered candidates for initiation in treatment with voretigene neparvovec:

- Clinical diagnosis of hereditary retinal dystrophy (includes measurements of visual acuity, visual field, fundus, electrophysiological tests, colour tests, autofluorescence and optical coherence tomography)[10].
- Presence of confirmed biallelic mutations in the *RPE65* gene by genetic analysis in a certified laboratory. The mutations must be classified as pathogenic or probably pathogenic variants[a].
- Age 3 years or older[b].

The following criteria must be met for each eye to be treated:

- Visual acuity equal to or less than 20/60 or visual field less than 20 degrees at any meridian measured by III4e isopter or equivalent (both eyes).
- Sufficient viable retinal cells determined by at least one of the following options:
    - Central retinal thickness ≥ 100 µm at posterior pole, determined by optical coherence tomography (OCT). It is suggested that the presence of the outer retinal layers (photoreceptors) be confirmed by OCT.

[a] Pathogenic or probably pathogenic variants will be included based on the American College for Medical Genetics and Genomics 2015 classification (https://www.nature.com/articles/gim201530). This will be assessed individually by a committee of clinicians and geneticists.
[b] The safety and efficacy of voretigene neparvovec in children under 4 years of age and in patients ≥ 65 years of age has not been established.

- ≥ 3 retinal disc areas without atrophy or pigmentary degeneration within the posterior pole, assessed by ophthalmoscopy and/or fundus autofluorescence (FAF) and/or retinography.
- Remaining visual field within 30 degrees of fixation for an III4e isoptera or equivalent analysed by kinetic or Goldman campimeter.

  If kinetic campimetry is not available, static campimetry with a Humphrey perimeter can be considered, programmes 30-2 or 24-2 where a 10 dB stimulus is equivalent to a 4e stimulus in kinetic perimetry.

Patients to whom any of the following apply will not be considered candidates for treatment:

- Patients who have been treated with gene therapies or who have previously participated in gene therapy clinical trials
- Presence of eye conditions or systemic diseases that may interfere with the outcome of the treatment or with the surgical procedure (eye or periocular infections and/or active intraocular or other inflammations).
- Intraocular surgery within 6 months prior to voretigene neparvovec treatment
- Use of retinoid compounds or precursors at high doses in the previous 18 months.
- Pregnant women and patients who do not use effective contraception within 4 months prior to administration of the vector.

4. GENERAL CONSIDERATIONS FOR TREATMENT WITH VORETIGENE NEPARVOVEC

Luxturna is supplied in a 2 mL

single-dose vial containing 0.5 mL concentrate requiring 1:10 dilution under aseptic conditions prior to administration.

The treatment should be initiated and administered by a vitreoretinal surgeon with experience in macular surgery. The use of intraoperative OCT is recommended.

The method of preparation and administration described in the authorised product characteristics summary[7] should be carefully followed, along with all the instructions contained in the training materials for healthcare professionals that form part of the risk management plan for the medicinal product and that are published on the website of the

Spanish Agency for Medicines and Medical Devices[17,18].

Dosage and method of administration

Patients receive a single dose of 1.5 x 10_{11} vector genomes (vg) voretigene neparvovec in each eye. Each dose is administered 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 at least 6 days apart between each surgical procedure.

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, and in case of such infection the start of treatment must be postponed until after the patient has recovered Starting 3 days prior to the administration of Luxturna to the first eye, it is recommended that an immunomodulatory regimen is initiated following the schedule described in the summary of product characteristics. Initiation of the immunomodulatory regimen for the second eye should follow the same schedule and supersede completion of the immunomodulatory regimen of the first eye.

Immunogenicity

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

Elderly patients

The safety and efficacy of voretigene neparvovec in patients ≥ 65 years old have not been established. However, no adjustment in dosage is necessary in elderly patients.

Hepatic and renal impairment

The safety and efficacy of voretigen neparvovec in patients with hepatic or renal impairment have not been established. No dose adjustment is required in these patients.

Paediatric population

The safety and efficacy of voretigene neparvovec in children aged up to 4 years have not been established. No data are available.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified organisms. Personal protective equipment should be worn while preparing or administering voretigene neparvovec. See instructions for preparation, accidental exposure and disposal of voretigene neparvovec.

Shedding

Vector shedding can occur at low levels and transiently through patients' tears. Patients and caregivers should be advised on how to properly handle waste materials generated from dressings, tears and nasal discharge. These handling precautions should be followed for 14 days after administration of voretigene neparvovec.

Other precautions

Patients should avoid air travel or other travel to high altitudes until the air bubble formed as a result of voretigene neparvovec administration has completely dissipated from the eye. A sudden increase in altitude while the air bubble is still present can cause an increase in eye pressure and irreversible loss of vision. Patients should avoid swimming due to an increased risk of eye infection and should avoid strenuous physical activity due to an increased risk of eye injury. Patients may resume swimming and strenuous activities after a minimum of one to two weeks, on the advice of their doctor.

5. EVALUATION AND MONITORING

The doctor responsible for the patient in each of the stages of the process must register the following information in VALTERMED.

General patient details (to be collected in VALTERMED before starting treatment to carry out the evaluation):

- NHS Code[c]
- CIP/CITE Code[c]
- NIF/NIE[c]
- Health Card No.[c]
- Medical Record No.:
- Sex[d]:
- Date of birth[d]:

Disease characterisation prior to beginning treatment

Clinical diagnosis (specify):

Confirmation of the biallelic mutation by genetic test: YES/NO. Date:

Evidence of viable retinal tissue determined by at least one of these three options:

- Central retinal thickness ≥ 100 µm at posterior pole, determined by optical coherence tomography (OCT). It is suggested that the presence of the outer retinal layers (photoreceptors) be confirmed by OCT.

  RE: Date: LE: Date:

- ≥ 3 retinal disc areas without atrophy or pigmentary degeneration within the posterior pole, assessed by ophthalmoscopy and/or fundus autofluorescence (FAF) and/or retinography.

  RE: Date and test performed: LE: Date and test performed:

- Remaining visual field within 30 degrees of fixation for an III4e isoptera or equivalent analysed by kinetic or Goldman campimeter. If kinetic campimetry is not available, static campimetry with a Humphrey perimeter can be considered, programmes 30-2 or 24-2 where a 10 dB stimulus is equivalent to a 4e stimulus in kinetic perimetry.

  RE: Date and test performed: LE: Date and test performed:

Full field light stimulus threshold (FST) test results using

[c] It is mandatory to fill in at least one of these fields.
[d] Mandatory fields.

white light [Log10 (cd.s/m_2)]:

RE: Date: LE: Date:

Visual Acuity (VA) [LogMAR][e]:

Indicate the optotype used: Snellen/Pigassou

RE: Date: LE: Date:

Visual field (Humphrey or Goldman):

RE: Date and test performed: LE: Date and test performed**:**

Voretigene neparvovec administration

- Date of administration RE: Date of administration LE:
- Dose administered: RE: LE:
- Intraoperative OCT check (yes/no) RE: LE:
- Failed to perform or complete administration (specify cause): RE:
  Date: LE: Date

Monitoring

The following clinical results should be recorded at **3, 6 and 12 months after administration and thereafter on an annual basis (+/- 15 days)** after administration of voretigene neparvovec and for each of the treated eyes:

- Full field light stimulus threshold (FST) test results using white light [Log10 (cd.s/m_2)]:
  RE: Date: LE: Date
- Visual Acuity (VA) [LogMAR][d]:
  Indicate the optotype used: Snellen/Pigassou RE:
  Date: LE: Date
- Change in the visual field: perimetry with Goldman or Humphrey
  RE: Date and test performed: LE: Date and test performed:
- Change in number of viable retinal cells by at least one of the three techniques described above: stabilisation, worsening, improvement or not

[e] Visual acuity should be assessed using the method appropriate to the age of the patient. Through the Snellen test in children and adults from 5 years and the drawing test (Pigassou) in children under 5 years. For standardisation purposes, all primary source visual acuity assessments will be converted to decimals and then LogMAR values using the following Holladay formula (1997): LogMAR = - Log (Decimal acuity).

assessable.

RE: Date and test performed: LE: Date and test performed:

Safety

Voretigen neparvovec is a medicinal product subject to additional monitoring. All legal obligations relating to safety monitoring must be followed, including the reporting of suspected adverse reactions through the Spanish Pharmacovigilance System (SEFV): www.notificaram.es

Recording adverse reactions in VALTERMED does not exempt from the obligation to report them through the SEFV in accordance with current legislation.

For the purposes of this protocol, adverse events potentially related to treatment or the administration procedure will be recorded whenever they are considered relevant. In particular, the following must be recorded:

- Increased in intraocular pressure
- Retinal tearing
- Retinal detachment
- Macular alterations
- Cataracts
- Intraocular inflammation and/or procedure-related infection
- Immune reaction
- Vitreous, retinal or subretinal bleeding
- Other

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