HAUTE AUTORITÉ DE SANTÉ

OPHTHALMOLOGY
New medicinal product
April 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

LUXTURNA (voretigene neparvovec), gene therapy

High clinical benefit in inherited retinal dystrophy caused by biallelic RPE65 mutations and substantial clinical added value in the therapeutic strategy

Main points

- LUXTURNA has a MA 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.
- It is the first treatment proposed in this orphan disease. It is a gene therapy targeting the RPE65 gene encoding an isomerase (RPE65 protein) involved in the restoration of photopigments in the cones (rhodopsin) and rods (iodopsin).
- It significantly improved the functional vision of patients, assessed via multi-luminance mobility testing (MLMT), one year after treatment of both eyes.
- The decision to initiate treatment should be the subject of a multidisciplinary team meeting and should be based on an array of tests, in particular to determine a sufficient number of viable cells.

Therapeutic strategy

- Current treatment is hinged around lifestyle and dietary measures (avoidance of toxins, antioxidant vitamin and omega 3 supplements, wearing of filter lenses, etc.) in the hope of slowing down the degenerative process, monitoring and treatment of ophthalmic complications (cataract, macular oedema) and psychological support for patients. Vitamin A palmitate and lutein-DHA are used as protective antioxidants. Their beneficial effect is the subject of much debate and their prescription in women of reproductive age should be particularly carefully monitored. Acetazolamide via the oral route or topical dorzolamide are used to reduce cystoid macular oedema.
- At more advanced stages of the disease, low-vision aids are useful to maximise residual visual acuity. Thereafter, palliative methods are available (white stick, use of guide dogs). Medical devices, such as ARGUS II57 and IRIS II58 prostheses and the RETINA IMPLANT ALPHA AMS59 subretinal implant, are subject to exceptional funding in France for patients with advanced-stage retinal degeneration. However, they are not suitable for patients with inherited retinal dystrophy caused by biallelic RPE65 mutations, who generally have no visual memory and have nystagmus, contraindicating the use of these devices.
- **Role of the medicinal product in the therapeutic strategy**

  LUXTURNA is a first-line treatment in the disease targeted by its indication.

  The decision to initiate treatment should be the subject of a multidisciplinary team meeting and should be based on an array of tests, in particular to determine a sufficient number of viable cells, including a genetic test, imaging exams (optical coherence tomography, adaptive optics), electroretinogram and psychophysiological tests such as pupillometry, visual acuity, visual field and multi-luminance mobility testing (MLMT).

Clinical data

- LUXTURNA has been granted a MA in all types of inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations. Only patients diagnosed with Leber congenital amaurosis with biallelic RPE65 mutations were included in the study (randomised, open-label, multicentre), which evaluated the efficacy and safety of voretigene neparvovec compared to the absence of treatment. It is currently accepted that these diseases form a phenotype

continuum of the same disease, enabling extrapolation of the results of this study to all inherited retinal dystrophies with biallelic RPE65 mutations.

- The efficacy of voretigene neparvovec was assessed in terms of improvement in visual function via a Multi-Luminance Mobility Test (MLMT) over a course with obstacles of varying heights. This test is suitable for patients in whom the visual loss is peripheral initially, then central. The difference between the group treated with voretigene neparvovec and the untreated group was +1.6 point for the MLMT score, ranging from -1 to +6 points, -1 point corresponding to successful navigation of a course with an illumination of 400 Lux and + 6 point corresponding to passing the course with an illumination of 1 Lux. Almost 2/3 of patients in the treated group passed the course with an illumination of 1 Lux whereas all the patients in the untreated group failed it.
  The improvement in score was obtained from the 30th day and was maintained after 1 year of follow-up (primary endpoint assessment time) and follow-up data over 2 to 4 years suggest that efficacy is maintained over this period.
- The adverse events were mainly related to the administration procedure with, in particular, potentially serious risks of increased intraocular pressure, retinal tear, macular hole, maculopathy and eye inflammation, endophthalmitis (1 case reported during the study). A risk of immunogenicity against viral capsid and the RPE65 protein should be considered in the medium and long term, although the short-term data are reassuring.

Special prescription requirements

- Medicinal product for hospital use only.
- Prescription reserved for ophthalmology specialists.
- Treatment must be initiated and administered by a specialised retinal surgeon experienced in the performance of macular surgery.

Benefit of the medicinal product

- The actual clinical benefit* of LUXTURNA is high
- LUXTURNA provides clinical added value** (CAV II, substantial) in the current therapeutic strategy.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 03 April 2019 (CT-17535) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".