NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of voretigene neparvovec within its marketing authorisation for treating inherited retinal dystrophies caused by RPE65 gene mutations.

Background

Inherited retinal dystrophies are a group of eye diseases caused by gene mutations which result in the gradual degeneration of the light sensitive cells (photoreceptor cells) on the back of the eye (the retina). There are 2 main types of photoreceptor cells: rods and cones. Rods are found in the outer regions of the retina and are responsible for peripheral and night vision. Cones make up the central part of the retina (the macula) and are responsible for colour vision and perception of fine detail. Mutations in more than 200 different genes have been identified as the cause of inherited retinal dystrophies. Mutations in the 65 kDa retinal pigment epithelium (RPE65) gene are associated with 2 types of inherited retinal dystrophy: retinitis pigmentosa, which primarily affects rods, and Leber's congenital amaurosis (LCA), which affects both rods and cones.

Retinitis pigmentosa initially causes loss of peripheral vision and problems seeing at night-time. Symptoms usually start between the age of 10 and 30, but could present earlier. As the disease progresses, central vision and colour vision are affected. It can lead to blindness. LCA is the most severe form of inherited retinal dystrophy and symptoms start at a younger age; children with LCA have profound sight impairment either at birth or within the first year of life. Complications of inherited retinal dystrophies include cataracts and glaucoma.

Retinitis pigmentosa accounts for around half[1] of inherited retinal dystrophies and the prevalence is around 20 to 30 people per 100,000[2-6]. LCA is less common, affecting 2 to 3 people per 100,000[7]. Mutations in the RPE65 gene account for 2% of retinitis pigmentosa and 6 to 16% of LCA diagnoses[8,9].

There are no treatments available for inherited retinal dystrophies. Management focuses on psychological support and visual rehabilitation, for example teaching people how to use aids for low vision. Wearing sunglasses to protect the retina for ultraviolet light may help preserve vision.

The technology

Voretigene neparvovec (Luxturna, Spark Therapeutics) is a gene therapy that treats specific forms of inherited retinal dystrophies caused by mutations in the RPE65 gene. It is injected directly into the retina by a surgeon.

Voretigene neparvovec does not currently have a marketing authorisation in the UK. It has been studied in clinical trials, compared with no intervention, in both eyes in people aged 3 years and over with LCA due to RPE65 mutations.

Intervention(s)	Voretigene neparvovec
Population(s)	People with inherited retinal dystrophies caused by RPE65 gene mutations
Comparators	Best supportive care
Outcomes	The outcome measures to be considered include: • best corrected visual acuity (both eyes) • visual field • contrast sensitivity • photosensitivity • need for cataract surgery • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The use of voretigene neparvovec is conditional on the presence of RPE65 gene mutations. The economic modelling should include the costs associated with diagnostic testing for RPE65 gene mutations in people with inherited retinal dystrophies who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Interventional Procedures**: Insertion of a subretinal prosthesis system for retinitis pigmentosa (2015). NICE interventional procedures guidance 537. Insertion of an epiretinal prosthesis for retinitis pigmentosa (2015). NICE interventional procedures guidance 519. **Related NICE Pathways:** Retinal and macular conditions (2016) NICE pathway https://pathways.nice.org.uk/pathways/eye-conditions
Related National Policy	NHS England, Manual for prescribed specialised services 2016-2017 (published 2016): chapters 12 (adult specialist ophthalmology services) and 120 (specialist ophthalmology services for children). https://www.england.nhs.uk/commissioning/wp-

	content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 2,4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

How are the services for inherited retinal dystrophies organised in the NHS? Is it expected that voretigene neparvovec would be delivered within the existing framework of services, or would new treatment centres be required?

How many people in England have inherited retinal dystrophies caused by RPE65 gene mutations? How many new cases are diagnosed each year in England?

Would voretigene neparvovec be expected to be used for both types of inherited retinal dystrophies caused by RPE65 (that is, retinitis pigmentosa and Leber's congenital amaurosis [LCA])? Should retinitis pigmentosa and LCA be examined separately?

Are people with inherited retinal dystrophies in England routinely tested for genetic mutations? How are RPE65 mutations diagnosed in practice? Are the diagnostic tests routinely available in current NHS practice in England?

Is it anticipated that voretigene neparvovec would be used in neonates, babies and young children?

Have all relevant comparators for voretigene neparvovec been included in the scope? Which treatments are considered to be established clinical practice in the NHS for inherited retinal dystrophies? How should best supportive care be defined?

Are the outcomes listed appropriate? Are there any other outcomes that should be included? Are functional measures of vision, such as mobility testing (a functional test involving a maze of arrows and obstacles, to assess visual field, visual acuity, light perception and contrast sensitivity), useful in practice?

Are there any subgroups of people in whom voretigene neparvovec is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider voretigene neparvovec will fit into the existing NICE pathway on retinal and macular conditions?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which voretigene neparvovec will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider voretigene neparvovec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of voretigene neparvovec can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 Daiger SP, Sullivan LS, Bowne SJ (2013) Genes and mutations causing retinitis pigmentosa. Clin Genet 84: 132–41.

2 Orphanet (2014) Retinitis pigmentosa. Accessed May 2017.

3 Bundey S and Crew SJ (1984) A study of retinitis pigmentosa in the City of Birmingham. J Med Genet 21: 417–20.

4 Haim M (2002) Epidemiology of retinitis pigmentosa in Denmark. Acta Ophthalmol Scand 80: 1–34.

5 Marlhens et al. (1998) Autosomal recessive retinal dystrophy associated with two novel mutations in the RPE65 gene. Eur J Hum Genet 6: 527–31

6 den Hollander et al. (2010) Lighting a candle in the dark: advances in genetics and gene therapy of recessive retinal dystrophies. J Clin Ivest 120: 3042–53.

7 Orphanet (2015) Leber congenital amaurosis. Accessed May 2017.

8 Cai X, Conley SM, Naash, MI (2009) RPE65: Role in the visual cycle, human retinal disease, and gene therapy. Opthalmic Genet 30: 57–62.

9 Cideciyan AV (2010) Leber Congenital Amaurosis due to *RPE65* Mutations and its Treatment with Gene Therapy. Prog Retin Eye Res 29: 398–427.