22 November 2018
EMA/810611/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Luxturna (Adenovirus-associated viral vector serotype 2 containing the human *RPE65* gene)

Treatment of inherited retinal dystrophies

EU/3/12/981 (EMA/OD/150/11)

EU/3/15/1518 (EMA/OD/040/15)

Sponsor: Spark Therapeutics Ireland Ltd

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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Introductory comment

The COMP considered that the granted orphan designations “treatment of Retinitis pigmentosa” and “treatment of Leber Congenital Amaurosis” should be renamed under the umbrella condition of “inherited retinal dystrophies”. The therapeutic indication “ Luxturna is indicated 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” falls entirely within the condition “inherited retinal dystrophies”.

1. Product and administrative information

EU/3/12/981

Product	
Active substance	Adenovirus associated viral vector serotype 2 containing the human *RPE65* gene
International Non-Proprietary Name	Voretigene neparvovec
Orphan indication	Treatment of Leber's congenital amaurosis
Pharmaceutical form	Solution for injection
Route of administration	Intraocular use
Pharmaco-therapeutic group (ATC Code)	--
Sponsor's details:	Spark Therapeutics Ireland Ltd The Tower Trinity Technology & Enterprise Campus Pearse Street Dublin 2 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Alan Boyd Consultants Ltd
COMP opinion date	8 February 2012
EC decision date	2 April 2012
EC registration number	EU/3/12/981
Post-designation procedural history	
Transfer of sponsorship	Transfer from Alan Boyd Consultants Ltd to Spark Therapeutics Ireland Ltd – EC decision of 09 March 2017

EU/3/15/1518

Product	
Active substance	Adenovirus-associated viral vector serotype 2 containing the human *RPE65* gene
International Non-Proprietary Name	Voretigene neparvovec
Initial orphan indications	Treatment of retinitis pigmentosa
Pharmaceutical form	Solution for injection
Route of administration	Intraocular use
Pharmaco-therapeutic group (ATC Code)	--
Sponsor's details:	Spark Therapeutics Ireland Ltd The Tower Trinity Technology & Enterprise Campus Pearse Street Dublin 2 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Alan Boyd Consultants Ltd
COMP opinion date	18 June 2015
EC decision date	28 July 2015

EC registration number	EU/3/15/1518
Post-designation procedural history	
Transfer of sponsorship	Transfer from Alan Boyd Consultants Ltd to Spark Therapeutics Ireland Ltd – EC decision of 09 March 2017

Marketing authorisation procedural history

Rapporteur / co-Rapporteur	Christiane Niederlaender, Sol Ruiz
Applicant	Spark Therapeutics Ireland Ltd
Application submission date	29 July 2017
Procedure start date	17 August 2017
Procedure number	EMA/H/C/004451
Invented name	Luxturna
Therapeutic indication	Luxturna is indicated 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. Further information on Luxturna can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/luxturna
CHMP opinion date	20 September 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	M. Možina/ D. O'Connor
Sponsor's report submission date	1 August 2017 - update 1 June 2018
COMP discussion and adoption of list of questions	6 August 2018
Oral explanation	12 September 2018
COMP opinion date	11 October 2018

2. Grounds for the COMP opinions at the designation stage

EU/3/12/981

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2012 was based on the following grounds:

- Leber's congenital amaurosis (hereinafter referred to as "the condition") was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating due to loss of visual acuity;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

EU/3/15/1518

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2015 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing adenovirus-associated viral vector serotype 2 containing the human *RPE65* gene was considered justified based on preclinical data supporting improvements in visual function following treatment with the product;
- the condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progresses to total blindness;
- the condition was estimated to be affecting less than 3.7 in 10,000 persons in the European Union, at the time the application was made;
- The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The applicant had received two orphan medicinal product designations: "treatment of Leber's Congenital Amaurosis" and "treatment of Retinitis Pigmentosa". The therapeutic indication is "treatment of patients with vision loss owing to autosomal recessive inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells".

In order to establish that the therapeutic indications falls entirely within the designated indications,. the applicant was requested to justify the scope of the indication in writing and during an oral explanation before the COMP. In response, and during an oral explanation before the COMP the

applicant noted that other (than RP and LCA) clinical diagnoses have been used to describe phenotypes of inherited retinal dystrophy associated with biallelic RPE65 mutations, including juvenile (Lorenz et al 2000 Invest Ophthalmol Vis Sci; 41; 2735-42), early onset retinitis pigmentosa (Walia et al 2010 Ophthalmology; 117:1190-8), early onset severe retinal dystrophy (EOSRD) (Paunescu et al 2005 Arch Clin Exp Ophthalmol; 243:417-26), severe early childhood onset retinal dystrophy (SECORD) (Weleber et al 2011 Invest Ophthalmol Vis Sci; 52:292-302), and autosomal recessive childhood-onset severe retinal dystrophy (arCSRD) (Gu et al 1997 Nat Genet; 2:194-7). However such diagnoses were not considered distinct conditions, and were generally on the basis of preferences of individual ophthalmologists rather than standardized phenotypic characteristics. The sponsor further posited that all these clinical diagnoses were in essence attenuated forms of LCA.

The COMP acknowledged that in the field of inherited retinal dystrophies, a given mutation may give rise to more than one clinical phenotypes, and considered that the proposed orphan conditions should be combined and renamed as “inherited retinal dystrophies”, covering both syndromic and non-syndromic retinal degenerations irrespectively of the involved mutations.

The orphan indications were therefore reworded as “treatment of inherited retinal dystrophies” and the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

Retinitis pigmentosa is a highly variable disorder with some patients developing symptomatic visual loss in childhood and others remaining asymptomatic until mid-adulthood (Hartong et al, Lancet. 2006;368(9549):1795). The typical course of RP is gradual development of visual field scotomas, acuity and symptomatic nyctalopia, preceded by ERG changes. Central retinal function declines more slowly (Holopigian K et al. Ophthalmology. 1996;103(3):398) and patients meet criteria for legal blindness by age 40 due to narrowing of visual fields (Hartong et al, Lancet. 2006;368(9549):1795). Retinitis pigmentosa is chronically debilitating due to the development of nyctalopia and tunnel vision that progresses to total blindness.

Similarly, Leber’s Congenital Amaurosis is acknowledged to be chronically debilitating due to loss of visual function. Leber congenital amaurosis is the most severe kind of inherited retinal diseases accounting for approximately 5% of the whole retinal dystrophies and 20% of the children that study on blind schools. Clinical ophthalmologic findings including severe vision loss, nystagmus and ERG abnormalities through the first year of life (Chacon-Camacho and Zenteno, World J Clin Cases, 2015. 3(2): p. 112-24.)

The COMP considered that the loss of vision is a common characteristic of all inherited retinal dystrophies, as discussed above for RP and LCA, which justifies their chronically debilitating feature.

Number of people affected or at risk

With regards to Retinitis Pigmentosa, the sponsor conducted a literature review, yielding estimates of prevalence ranging from 0.6 to 3.3 per 10,000. The applicant cited Orphanet Report Series (January 2018) referring to a worldwide prevalence of RP as 2.67 per 10,000. OMIM and NIH databases have also been searched by the applicant; they most commonly cite the prevalence estimates of 1 in 3,000 to 1 in 5,000 (accessed 17 May 2018).

As for Leber's Congenital Amaurosis, the applicant has conducted a literature and database (NIH, NORD, Orphanet) review. The papers reviewed supported a less than 1 in 10,000 estimate (please refer to the embedded maintenance report), while The National Institutes of Health Gene Review publication titled "Leber Congenital Amaurosis" (Weleber et al., last updated May 2013) quotes a prevalence for LCA of 2-3 per 100,000 births. Similarly, the same figures are provided by Genetics Home Reference (NIH) website. A prevalence of 1-2 per 100,000 births is cited in a report on Leber Congenital Amaurosis published by the National Organisation for Rare Disorders (NORD) (NORD report 2017). The Orphanet database, provides the same values of 2.5 per 100,000 (equivalent to 0.25 per 10,000) for estimated prevalence and birth prevalence of Leber congenital amaurosis worldwide (Orphanet Report Series, January 2018).

In writing and during the oral explanation, the applicant was invited to amend the estimate accordingly to account for all inherited retinal dystrophies. To that end, the applicant estimated the prevalence of "inherited retinal dystrophies" to be approximately 3 per 10,000 with reference to a Danish epidemiological study (Bertelsen M, Jensen H, Bregnhoj JF, et al (2014) Prevalence of generalized retinal dystrophy in Denmark. Ophthalmic Epidemiol; 21:217-23). The COMP accepted this conclusion for the maintenance of the orphan designation. It was also considered the previously considered estimates for RP and LCA in the context of previous designations (approximately 3 and less than 1 in 10,000 respectively), represented conservative approaches and were in line with the conclusions of this study, which was comprehensive and complete.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

For Inherited retinal dystrophies, no authorised products were identified in the EU. The sponsor noted that for Retinitis pigmentosa nutritional/dietary recommendations include supplementation with vitamin A and fish oils, modulation of light exposure and supportive treatment via rehabilitation centres. (Hartong et al, Lancet. 2006;368(9549):1795). Similarly for LCA, the applicant did not identify any authorised products in the EU for the treatment of the condition. Care remains supportive and confined to correction of refractive error, use of low vision aids and access to educational and work-related opportunities (Weleber et al., 2010). The COMP agreed that no authorised products currently exist in the EU.

Significant benefit

Not applicable.

4. COMP opinion adopted on 11 October 2018

The COMP concluded that:

- the orphan indications should be combined and reworded as "treatment of inherited retinal dystrophies";
- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;

- the prevalence of inherited retinal dystrophies (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be approximately 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to loss of vision;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Luxturna, adenovirus-associated viral vector serotype 2 containing the human *RPE65* gene, voretigene neparvovec, EU/3/12/981 and EU/3/15/1518 for treatment of inherited retinal dystrophies is not removed from the Community Register of Orphan Medicinal Products.