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Our reference
2020001290

Date 17 February 2020
Subject Package advice voretigene neparvovec (Luxturna®)

Dear Mr Bruins,

In this letter, Zorginstituut Nederland advises you about voretigene neparvovec (Luxturna®) for the treatment of vision loss due to inherited retinal dystrophy with bi-allelic RPE65 mutations. The reason for this assessment was the placing of voretigene neparvovec (Luxturna®) in the package lock for expensive medications

General

From the point of view of the basic package paid from joint premiums, the Zorginstituut makes the assessment of whether new care should be part of the insured package. We are weighing this, both scientifically and in terms of social support, and we are weighing aspects of efficiency and transparency. The Zorginstituut is advised by two independent committees: The Scientific Advisory Council (WAR) for the scientific and practical assessment of the data and the determination of the cost-effectiveness and the Package Advisory Committee (ACP) for the social assessment. We also consulted interested parties during the assessment process.

The Zorginstituut assessed voretigene neparvovec on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. With this letter, I would like to inform you about the result of the full weighting of these package criteria.

Integral package criteria weighting

The Zorginstituut considers that voretigene neparvovec complies with the legal criterion '*current state of science and practice'* for the above indication.
Below is a list of the relevant aspects of the medication, which play a role in our weighting. Firstly, it is relevant that this is a one-time gene therapy that is injected into the subretinal spacevia surgery under anaesthesia. After administration, a significant and relevant improvement in functional vision was

[1] Real-world package management 3 (2013). Zorginstituut Netherlands, Diemen. Via www.zorginstituutnederland.nl

[2] Current state of science and practice assessment: updated version (2015). Zorginstituut Netherlands, Diemen. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness report (2015). Zorginstituut Netherlands, Diemen. Via www.zorginstituutnederland.nl

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observed in patients with poor vision and the presence of sufficiently viable retinal cells. However, there was no recovery of normal vision. It is not yet clear how long the effect lasts and whether further deterioration will be countered. This data is lacking. This is an uncertainty that we have taken into account. We realize that it may be very important for a patient that the disease progress is halted, because that means that they will remain self-sufficient longer, and remain able to work or finish a training program, for instance. The adverse effects on the short term were limited to mild to moderate ocular side-effects; one patient had loss of visual acuity in the first treated eye .

There is no *cost-effectiveness* model of sufficient quality available. We consider this to be serious, but we note that, on the basis of the currently available data, a short-term reassessment will not lead to other insights. This is linked, among other things, to the mentioned uncertainty in the long-term effects. The burden of disease cannot be properly determined, but is expected to be high if the psychological side of the disease is taken into account.

The *cost* per patient for treatment of both eyes is €690,000. A total of 28 patients (four of which have already been treated in one eye) are expected to be eligible for treatment with voretigene neparvovec (Luxturna®) in the first year after inclusion in the package. One incident patient is added annually. The application of voretigene neparvovec (Luxturna®) will mean an estimated cumulative cost of €19.3 million in the third year, €19.5 million when also taking into account the administration costs. Repeated administration of voretigene neparvovec does not seem to be applicable here, as this is not expected to be possible due to the poor condition of the eye.

Since this is a one-off treatment, it is not yet certain how these costs will be charged to the basic package in the first three years after market introduction. This depends on the rate at which prevalent patients will be treated. When the prevalent patients have all been treated, the estimated budget impact will decrease to €700,000 per year.

With the currently available packaging of voretigene neparvovec, more than 90% of the product is wasted. A large part of the budget impact could be avoided if the product could be used for multiple administrations. The medical profession has mentioned this as a possible option. The additional costs are estimated at €9.6 million in the third year after inclusion in the package if two patients could be treated with one injection phial.

Package advice

The treatment meets the ‘current state of science and practice’ criterion, but looking at the great uncertainties about the long-term effects of this gene therapy and about the cost-effectiveness, the Zorginstituut advises you to only admit the treatment to the package if the price can be significantly reduced. In your price negotiations, we ask you to particularly take into account the above-mentioned uncertainty of this gene therapy. A pay for performance agreement, whereby agreements are made about step-by-step compensation linked to the degree of effectiveness and the available burden of proof, would be a very relevant option. Novartis has indicated that they are open to such an agreement.

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Proper use
Upon inclusion in the basic package, the Zorginstituut will conclude an orphan drug arrangement with the parties, which will establish agreements on appropriate use, an indication committee, data collection and evaluation by means of an international register (given the rarity of the disease). The first steps have already been taken by the parties. We will continue to guide this process. The Zorginstituut points out that it is important that centres of excellence have sufficient resources to meet the commitments made and to be able to follow the practice properly.
Partly because of the rarity of the disease, the Zorginstituut considers centralization in one centre to be appropriate.

Evaluation
If voretigene neparvovec is admitted into the insured package on the basis of the outcome of the price negotiation, the Zorginstituut will actively monitor its use. The basis for this will be the orphan drug package, concluded by physicians, hospitals, health insurers and patients.
We will inform you about the result of the practical use in 2025. In the context of the treatment landscape, the Zorginstituut takes the following points into consideration:

- The initial estimate of the number of patients compared to the actual number treated;
- The cost development compared to the original cost estimate;
- The realisation of an orphan drug arrangement and compliance with this orphan drug arrangement.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

Appendices
ACP advice
Pharmaco-therapeutic report for voretigene neparvovec (Luxturna®)
Budget impact analysis for voretigene neparvovec (Luxturna®)
Pharmaco-economic analysis voretigene neparvovec (Luxturna®)