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**National Health Care Institute**
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**Contact**
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*2021016504*

**Our reference**
2021016504

Date 6 May 2021
Subject Packet advice package lock medicinal product onasemnogene abeparvovec (Zolgensma®)

Dear Ms van Ark,

The National Health Care Institute advises you on onasemnogene abeparvovec (Zolgensma®) in the treatment of patients with symptomatic spinal muscular atrophy (SMA) type 1 and presymptomatic SMA patients with up to three copies of the SMN2 gene. The reason for this advice was the placing of the above-mentioned medicinal product in the so-called lock procedure for expensive medicines. The National Health Care Institute carried out the assessment within the 'Beneluxa Initiative' and collaborated with Belgium and Ireland.

Onasemnogene abeparvovec (OA) is an innovative, promising and one-time treatment that addresses the cause of the disease and meets the established medical science and medical practice. This gene therapy is very important for the treatment of a life-threatening condition in very young children. The first results are promising; pre-symptomatic treatment seems to prevent the disease. That is valuable.
However, there are also great uncertainties about the effects, both in the short and long term and about the possible use of additional disease-modifying treatments. Furthermore, the cost-effectiveness based on the available data is uncertain and as yet unfavourable. Data collected in the future in the existing SMA register will provide more information about this.
The National Health Care Institute advises you to include OA in the health insurance package when the following conditions are met:

- On the basis of the above-mentioned uncertainties, the risk of overpricing should not be placed exclusively with those paying the premiums. Taking into account a price reduction of 85% for nusinersen (the current treatment) and uncertainty about effectiveness, a price reduction of 91% should apply to OA to arrive at a cost-effective treatment with OA. If the marketing authorisation holder's claim is fully realised, no price reduction would be necessary. If that risk were shared, a price reduction of approximately 50% would be required.
- In addition, the National Health Care Institute recommends a 'pay for performance' agreement whereby the payment depends on whether or not relevant outcome measures are reached. The following relevant outcome measures may be part of this agreement:
  - the use of additional disease-modifying treatments such as, for

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example, nusinersen;
- ventilation-free survival;
- reaching motor milestones.

The National Health Care Institute advises you to enter into the (price) negotiations within the already existing Beneluxa collaboration. In 5 years' time, the National Health Care Institute could reassess how the cost-effectiveness has developed on the basis of the data available.

In this letter, I explain our findings and final conclusion.

## General

At your request, the National Health Care Institute assesses whether new care should be part of the insured package. The National Health Care Institute bases its decision from the perspective of the health insurance package paid from joint premiums. The National Health Care Institute has assessed OA on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. We take into consideration the degree of certainty that this will be achieved, both in the scientific sense, as well as in terms of public support, and we consider the efficiency and transparency aspects. The National Health Care Institute is advised in its package assessments by two independent committees:

- The Scientific Advisory Board (WAR) for the review of data according to the established medical science and medical practice, and to determine the cost-effectiveness; and
- The Insured Package Advisory Committee (ACP) for the social assessment.

We also consulted stakeholders during the assessment process.

## Onasemnogene abeparvovec (Zolgensma®)

Patients with SMA have a defect in the SMN1 gene. The body needs this gene to produce a protein that is essential for the normal functioning of the nerves that control muscle movements. The active substance in OA contains a functional copy of this gene. When injected, the product (through an AAV vector) passes into the nerves from where it delivers the right gene to produce sufficient protein to safeguard the nerve function. In addition to the SMN1 gene, the SMN2 gene also produces a small part of the required protein. The number of SMN2 copies is the most important determining factor for the severity of SMA, but not the only one. The indication of OA as determined by the EMA includes the treatment of:

- patients with 5q spinal muscle atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1; and
- patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

The requested reimbursement is narrower and is supported by the physicians association:

- all symptomatic patients with SMA type 1;
- presymptomatic SMA patients with up to 3 copies of the SMN2 gene.

Nusinersen was the first medicinal product approved for the treatment of SMA in 2017. Treatment with nusinersen (regardless of the type of SMA) is reimbursed

[1] Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[2] Established medical science and medical practice assessment: updated version (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

for children who start treatment before the age of 9.5 years. From 9.5 years onwards, nusinersen is available via conditional inclusion.

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**Integral weighting of package criteria**

*Symptomatic patients with SMA type 1*

In the most important completed STR1VE-US study, 20 (90%) of the 22 babies who were treated with OA were still alive after 14 months and breathed without a permanent ventilation machine. Normally, only a quarter of untreated patients would survive without a permanent ventilation machine. The SHINE study with nusinersen showed that 32 (37%) of the 63 babies were still alive after 18 months and breathed without a permanent ventilation machine.
The STR1VE-US study also showed that OA can help babies in sitting without assistance for at least 30 seconds. 14 of the 22 babies who received OA were able to do so after 18 months, a milestone that is never reached in untreated babies with severe forms of the disease. On all outcome measures in symptomatic patients (survival, ventilation-free survival and mobility), OA seems better than nusinersen. However, due to the lack of comparability of the studies (patients in the studies with nusinersen were worse at the start of treatment than in the OA studies), we cannot make a statement about a clinically relevant difference.

*Presymptomatic patients with 2 or 3 copies of the SMN2 gene*

Presymptomatic patients can be identified through older siblings or through neonatal (heel prick) screening. Neonatal screening is expected to start in the Netherlands in October 2022.
The SPR1NT study on the treatment of presymptomatic patients with OA has not yet been completed. So far, all treated patients (n=29) are still alive and breathing without a permanent ventilation machine (median follow-up is 15 months). In the cohort patients with 2 SMN2 copies, 11 out of 14 patients can sit without support (10 reached this milestone within the limits of normal development) and in the cohort patients with 3 SMN2 copies, 8 of the 15 patients can stand, and 6 of the 15 can walk.
Even after presymptomatic treatment with nusinersen (the NURTURE study), all patients have remained alive without permanent ventilation.
Longer follow-up is necessary to draw definitive conclusions on the effectiveness of OA compared to nusinersen.

*Established medical science and medical practice*

The National Health Care Institute, the Belgian Committee for the Reimbursement of Medicinal Products (CTG) and the Irish National Centre for Pharmacoeconomics (NCPE) conclude that OA meets the established medical science and medical practice for the treatment of symptomatic patients with SMA type 1. The mechanism of action, the broad consensus on the benefits of a presymptomatic treatment and the fact that more than half of patients with 3 copies of SMN2 will possibly develop a very serious disease, are considered sufficient to conclude that OA also meets the established medical science and medical practice for presymptomatic SMA patients with 2 or 3 copies of the SMN2 gene.
There is insufficient evidence to draw definitive conclusions on the effectiveness of OA compared to nusinersen. A good comparative study comparing OA with nusinersen has not been carried out and will probably not be carried out in the future.

*Budget impact*

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The net budget impact of OA in year 3 will be approximately €11 million in the Netherlands. This budget impact is highly dependent on the selected population and the costs and assumptions concerning the use of nusinersen.

*Cost-effectiveness*
The cost-effectiveness is determined for a subgroup of patients within the registered indication, i.e. symptomatic patients with SMA type 1. Presymptomatic patients are included in a scenario analysis.
The treatment effects of OA are probably overestimated due to the application of single-arm studies and model choices as made by the marketing authorisation holder, such as choices for (beneficial) long-term effects. The added value of OA in relation to nusinersen cannot yet be determined because comparative effectiveness data are missing.
The Beneluxa countries could not agree with the assumptions made in the model by the marketing authorisation holder and had an alternative 'base case' analysis performed, which included the use of nusinersen after administration of OA. The estimate of this 'incremental cost effectiveness ratio' (ICER) shows that OA is not cost-effective versus nusinersen or best support care (BSC); the estimated ICER is €263,389 per QALY versus nusinersen.
In a previous assessment, the cost-effectiveness of nusinersen was determined for the above indication. The price for nusinersen has been negotiated by the Minister. Because this information is not public, the National Health Care Institute has itself drawn up a scenario for the current assessment of OA's cost-effectiveness, based on the price of nusinersen recommended at the time (a price decrease of 85% to approach the reference value). In that case, the price of the OA must decrease by 91% to fall within the reference value of €80,000 per QALY.

**Orphan drug arrangement**
To monitor and track the deployment of OA, the existing orphan drug arrangement for nusinersen will be extended to include OA. It sets out agreements on start and stop criteria, an indication commission, data collection and evaluation. The existing SMA registry that is maintained by the SMA Expertise Centre is used as a basis. The National Health Care Institute will continue to facilitate this process. The National Health Care Institute points out that for the implementation of such orphan drug arrangements it is essential that centres of expertise have sufficient resources to meet the commitments made and to be able to follow the practice properly. This is the only way to obtain sufficient data for the recommended pay for performance.
The results of the orphan drugs arrangement will be published annually in the *Orphan Drugs Monitor in Practice*.
In addition, the data in the existing SMA register may provide the opportunity to gain more certainty about the long-term effectiveness of OA over time.

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**Final conclusion**

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- In addition, the National Health Care Institute recommends a 'pay for performance' agreement whereby the payment depends on whether or not relevant outcome measures are reached. The following relevant outcome measures may be part of this agreement:
  - the use of additional disease-modifying treatments such as, for example, nusinersen;
  - ventilation-free survival;
  - reaching motor skill milestones.

The National Health Care Institute advises you to enter into the (price) negotiations within the already existing Beneluxa collaboration. In 5 years' time, the National Health Care Institute could reassess how the cost-effectiveness has developed on the basis of the data available.

Yours sincerely,

Sjaak Wijma
*Chair of the Executive Board*