Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

Ministry of Health, Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

National Health Care Institute
Care
Medicinal Products

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
Ms J.M. van der Waal
T +31 (0)6 120 017 28

2022024106

Our reference
2022024106

Date 15 July 2022
Subject Package advice for the lock procedure drug risdiplam (Evrysdi®)

Dear Mr Kuipers,

The National Health Care Institute advises you on risdiplam (Evrysdi®) for the treatment of 5q spinal muscular atrophy (SMA) in patients aged 2 months of age and older with a clinical diagnosis of SMA type 1, type 2, or type 3, or with one to four SMN2 copies. The reason for this advisory report was the placing of the above-mentioned medicinal product in the so-called 'lock procedure' for expensive medicinal products.

Following risdiplam's placement in the lock procedure, the National Health Care Institute has assessed the reimbursement for this medicinal product. The marketing authorisation holder has submitted a dossier, in the context of the package management of inpatient medicines. During the assessment, the National Health Care Institute and the Ministry of Health, Welfare and Sport jointly came to the conclusion that, on the basis of the demarcation letter[1], risdiplam should be designated as an outpatient medicinal product. The medicinal product is a drink that the patient can take at home. However, the National Health Care Institute takes the view that, in the case of risdiplam, intramural funding is both logical and appropriate. These are highly specialised medicinal products that are prescribed from a single centre of expertise. To date, every medicinal product that has been made available for the treatment of SMA has been funded intramurally. The funding of all medicinal products via the same route creates a level playing field, and encourages appropriateness more effectively. The National Health Care Institute understands that, at the present time, the demarcation letter must be leading. However, it advises the Ministry of Health, Welfare and Sport to give broader consideration to the demarcation policy.

All 5q SMA patients lack a functional SMN1 gene. Thus, SMA patients rely on SMN2, a kind of 'spare' gene for the production of SMN protein. While this gene is very similar to SMN1, it produces much smaller amounts of functional SMN protein. Risdiplam corrects the splicing of SMN2, leading to the increased synthesis of functional and stable SMN protein. Risdiplam complies with

[1] Ministry of Health, Welfare and Sport (2014) Afbakening aanspraak Farmaceutische Zorg en aanspraak Geneeskundige Zorg met betrekking tot geneesmiddelen (Demarcation of entitlement to Pharmaceutical Care and entitlement to Medical Care with regard to medicinal products). (Reference number: 183496-115412-GMT

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established medical science and medical practice for the treatment of 5q SMA in patients from 2 months to 25 years of age, with a clinical diagnosis of SMA type 1, type 2, or type 3, and for presymptomatic patients with one to four copies of the SMN2 gene. Due to insufficient evidence, risdiplam does not (yet) comply with established medical science and medical practice for the treatment of 5q SMA in patients above 25 years of age, with a clinical diagnosis of SMA type 2 or type 3. There are also a number of uncertainties, especially with regard to this medicinal product's long-term effectiveness. Furthermore, based on the available data, its cost-effectiveness is uncertain and, as yet, unfavourable.

The National Health Care Institute advises you to include risdiplam in the health insurance package for indications that comply with established medical science and medical practice, subject to the condition that a price reduction is achieved. Based on the cost-effectiveness models, a discount of at least 86% would be required. However, given the risk of uncertainty and arguments regarding competition (risdiplam is neither the first – nor the only – medicinal product that is available for the treatment of SMA), a larger reduction in price would be justified. The Package Advisory Committee (ACP) considers an additional discount percentage of around 50% of the difference (100%-86% = 14% and half of that) to be appropriate, which would involve a price reduction of the order of 93%.

For the treatment of patients above 25 years of age with a clinical diagnosis of SMA type 2 or type 3, the National Health Care Institute, together with all of the stakeholders, will endeavour to make risdiplam available via conditional inclusion. The National Health Care Institute, the patients' association, and the physicians' association share the explicit wish that risdiplam be added to the current conditional inclusion process for nusinersen. This would mean that no extra budget needs to be arranged, provided the price of risdiplam is equal to or less than that of nusinersen.

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 health insurance package from the point of view of the basic health care package paid from joint premiums. The National Health Care Institute has assessed risdiplam on the basis of the four package criteria[2] of effectiveness[3], cost-effectiveness[4], necessity and feasibility. We consider these both in the scientific sense, as well as in terms of public support. We also review the aspects of efficiency and transparency. The National Health Care Institute is advised in its package reviews by two independent committees:

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

We also consulted stakeholders during the assessment process.

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

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

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

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Comprehensive weighting of package criteria

Established medical science and medical practice

The FIREFISH study investigated the use of risdiplam in symptomatic patients with SMA type 1. The results of this study show that after 12 months of treatment, 29% of the risdiplam cohort achieved the motor milestone of 'sitting without support'. Untreated patients with SMA type 1 never achieve this milestone. In addition, there is an increase in the chances of survival and the chances of ventilation-free survival. Substantial effects are seen in terms of increases in motor function and strength. Despite uncertainties caused by the study design and residual confounding, the National Health Care Institute concludes that, due to its substantial short-term effects, risdiplam for these patients complies with established medical science and medical practice.

The SUNFISH study investigated symptomatic patients (from 2 to 25 years of age) with SMA type 2 and type 3. The results of this study show that risdiplam has a desirable effect on the disease progression of SMA in these patients, especially with regard to motor function. Thus, for these patients too, risdiplam complies with established medical science and medical practice.

Given risdiplam's mechanism of action (it boosts functional SMN protein levels), in combination with the progressive course of SMA, it is expected that the greatest health gains can be achieved in the youngest patients, who have not yet accumulated any disease-related damage. Thus, it is uncertain whether, in patients above 25 years of age, (who were not included in the study) risdiplam has any added value in terms of slowing the progression of this disorder.

There are no published reports concerning risdiplam's effectiveness in presymptomatic patients with one to four copies of the SMN2 gene. The EMA granted registration, even though the effectiveness data for this group of young presymptomatic patients was not yet available. Children born with multiple copies of the SMN2 gene have a milder phenotype. This demonstrates that the pathophysiology of this disease is caused by the inadequate production of functional SMN protein. In addition, risdiplam appears to have a greater effect in patients with a shorter disease duration, whose muscle function has not yet been extensively impaired by the deficiency of SMN protein.

Like nusinersen and onasemnogene abeparvovec, risdiplam boosts functional SMN protein levels. The Dutch SMA physicians' association endorses the view that the most effective treatments are those that commence before any symptoms appear. Presymptomatic treatment will become even more relevant in the future, as SMA will be included in the Guthrie test (heel prick) screening from 1 June 2022. For presymptomatic patients too, risdiplam complies with established medical science and medical practice.

There is insufficient evidence to draw definitive conclusions about the effectiveness of risdiplam, as compared to nusinersen and onasemnogene abeparvovec (OA). No good quality controlled studies comparing risdiplam with nusinersen or OA have yet been carried out, nor is this likely to happen in the future.

Budget impact

The net budget impact of risdiplam in year 3 amounts to €5 million. This budget impact is highly dependent on the selected population and on the costs and assumptions surrounding the use of nusinersen (related to substitution). This is because, if the price of nusinersen is assumed to be 85% lower (as advised by the National Health Care Institute) than the pharmacy purchase price, the net budget impact of risdiplam will rise to €28 million.

Cost-effectiveness
The cost-effectiveness analyses of the marketing authorisation holder's model for type 1 SMA and for type 2/type 3 SMA are of sufficient methodological quality. However, there is some uncertainty about the long-term effects of risdiplam, the utilities, and the cost estimates. Furthermore, the cost-effectiveness analyses take no account of the cost-effectiveness of risdiplam following previous treatment with OA or nusinersen, due to the lack of relevant data. International guidelines do not recommend the use of combinations, as there is not yet any relevant evidence to support this. Future treatment dynamics are difficult to predict. The marketing authorisation holder reports the following incremental cost-effectiveness ratios (ICER) for risdiplam versus best supportive care:

- SMA type 1: €362,300 per QALY.
- SMA type 2/type 3: €416,471 per QALY.

With a relevant reference value for this disorder of €80,000 per QALY, risdiplam is not a cost-effective treatment. The price would have to decline by 94% (SMA type 1) and 78% (SMA type 2/type 3) to fall below the reference value of €80,000 per QALY.

Orphan drugs arrangement
To monitor and track the deployment of risdiplam, the existing orphan drugs arrangement for nusinersen and OA will be extended to include risdiplam. It sets out agreements on start and stop criteria, an indication committee, 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 guide 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. Only in this way can sufficient data be obtained. The results of the orphan drugs arrangement will be published annually in the *Orphan Drugs in Practice Monitor*.

Final conclusion
Risdiplam complies with established medical science and medical practice for the treatment of 5q SMA in patients from 2 months to 25 years of age, with a clinical diagnosis of SMA type 1, type 2, or type 3, and for presymptomatic patients with one to four copies of the SMN2 gene.

Due to insufficient evidence, risdiplam does not (yet) comply with established medical science and medical practice for the treatment of patients above 25 years of age, with a clinical diagnosis of SMA type 2 or type 3.

There are also a number of uncertainties, especially with regard to this medicinal product's long-term effectiveness. Furthermore, based on the available data, its cost-effectiveness is uncertain and, as yet, unfavourable.

The National Health Care Institute advises you to include risdiplam in the health insurance package for indications that comply with established medical science and medical practice, subject to the condition that a price reduction is achieved. Based on the cost-effectiveness models, a discount of at least 86% would be required. However, given the risk of uncertainty and arguments regarding competition (risdiplam is neither the first – nor the only – medicinal product that is available for the treatment of SMA), a larger reduction in price would be justified. The Package Advisory Committee (ACP) considers an additional discount percentage of around 50% of the difference (100%-86% = 14% and half of that) to be appropriate, which would involve a price reduction of the order of 93%.

For the treatment of patients above 25 years of age with a clinical diagnosis of SMA type 2 or type 3, the National Health Care Institute, together with all of the stakeholders, will endeavour to make risdiplam available via conditional inclusion. The National Health Care Institute, the patients' association, and the physicians' association share the explicit wish that risdiplam be added to the current conditional inclusion process for nusinersen. This would mean that no extra budget needs to be arranged, provided the price of risdiplam is equal to or less than that of nusinersen.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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