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2023041087

Date 20 December 2023
Re: GVS assessment of risdiplam (Evrysdi®)

Our reference
2023041087

Dear Mr Kuipers,

In July 2022, the National Health Care Institute advised you on the medicinal product risdiplam (Evrysdi®). The advice was to reimburse risdiplam (Evrysdi®) under conditions (List 2) from the basic health care package for insured persons

1. aged 2 months to 25 years (at the start of treatment) and with a clinical diagnosis of 5q SMA type 1, type 2 or type 3, or
2. with a presymptomatic diagnosis of 5q SMA and one to four copies of the SMN2 gene.

Recently, the indication for risdiplam (Evrysdi®) was extended. For the National Health Care Institute, this was the reason to give you additional advice on risdiplam (Evrysdi®).

Guiding principles of the assessment
In July 2022, the National Health Care Institute advised you that the treatment of 5q SMA in patients aged from 2 months to 25 years, 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, meets the established medical science and medical practice. 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.

The indication for risdiplam has recently been extended and this medicinal product has also been registered for children from 0 to 2 months of age. The marketing authorisation holder is requesting the inclusion of this product for children aged from 0 to 2 months in List 1B of the Health Insurance Regulation.

Registered indication
For the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA type 1, type 2, or type 3, or with one to four copies of the SMN2 gene.

5q spinal muscular atrophy (SMA)
SMA is a rare hereditary muscular disease. All 5q SMA patients lack a functional SMN1 gene. SMN1 on chromosome 5q encodes for SMN protein. SMN protein is essential for the performance and survival of motor neurons (nerve cells from the

spinal cord that control muscle movements). Absence or substantial deficiency of SMN protein causes degeneration of motor neurons in the spinal cord's motor anterior horn cells. Defective or no signals at all are transmitted to the muscles, resulting in paralysis and the thinning of muscles (atrophy). SMN protein is encoded by two genes: SMN1 and SMN2. 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. SMA patients have at least one copy of the SMN2 gene. Usually, the number of copies varies between one and four. In rare cases, an individual has eight copies. Having eight SMN2 copies protects against the development of SMA.

The rate of paralysis and muscular atrophy varies per type of SMA (SMA type 0 through SMA type 4). The type of SMA can be determined by the initial age, the motor milestones achieved and the number of copies of the SMN2 gene.

Risdiplam (Evrysdi®)
Risdiplam corrects the splicing of SMN2, leading to the increased synthesis of functional and stable SMN protein. Risdiplam is available as a powder for oral suspension. Each bottle contains 60 mg of risdiplam in 2 g powder for oral solution. Each millilitre of prepared solution contains 0.75 mg of risdiplam.

Risdiplam is taken orally once a day after a meal, always at the same time. The dose is determined by age and body weight (see **List 1**).

Alternatives
Currently, nusinersen (Spinraza®; intrathecal injection) and onasemnogene abeparvovec (Zolgensma®; gene therapy) are registered for children from 0 to 2 months of age. These two treatments are administered at the hospital. Risdiplam is an oral application for use at home. It has the added advantage that it can be started immediately after diagnosis. Administration of onasemnogene abeparvovec should be delayed in patients with elevated anti-AAV9 antibody titres or infections. In addition, treatment with onasemnogene abeparvovec is associated with safety concerns due to the related corticosteroid treatment. Due to the intrathecal route of administration, there are some safety concerns regarding nusinersen. In particular, for patients under 2 months of age where a severe phenotype is expected and immediate treatment can prevent damage, the European Medicines Agency (EMA) states that risdiplam fulfils an unmet treatment need.

Content assessment
The marketing authorisation holder claims that risdiplam for children aged from 0 to 2 months complies with the established medical science and medical practice. In its initial assessment, the National Health Care Institute already concluded that risdiplam for presymptomatic patients meets the established medical science and medical practice. Despite the lack of evidence of effectiveness of risdiplam in presymptomatic patients at the time of registration, it was registered for this group of patients. In the registration study of symptomatic patients with SMA type 2 and type 3, who were up to 25 years old, risdiplam showed the greatest effects in the youngest patients (2-5 years). As age progresses, the effectiveness seems to decrease, especially in young adults (18-25 years). 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

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be achieved in the youngest patients who have not yet accumulated any disease-related damage. The Dutch SMA professional group endorses the view that the most effective treatments are those that commence before any symptoms appear. Presymptomatic treatment is also relevant as SMA has been included in the Guthrie test (heel prick) screening since 1 June 2022. Based on these additional arguments, the National Health Care Institute concluded that risdiplam for presymptomatic patients meets the established medical science and medical practice.

Interim results of the ongoing Phase 2 clinical study RAINBOWFISH have since been published. This recently led to the extended market registration of risdiplam (for patients aged 0-2 months). The results from this study are particularly important for dose determination in patients under 2 months of age. In addition, this study provides information on the beneficial and adverse effects of risdiplam in infants aged 0 to 2 months (at the start of treatment) with presymptomatic SMA. In this letter, we assess this data to determine whether the previous assumption by the National Health Care Institute, that risdiplam is also effective in presymptomatic patients, is correct. In addition, we are considering whether the List 2 conditions can be extended and treatment of patients younger than 2 months with a clinical diagnosis of 5q SMA type 1, type 2 or type 3 is safe and also complies with the established medical science and medical practice.

RAINBOWFISH study
The RAINBOWFISH study is an ongoing open-label, multicentre, single-arm clinical trial to investigate the effectiveness, safety, pharmacokinetics and pharmacodynamics of risdiplam in infants from birth up to 6 weeks (at the first dose) who are genetically diagnosed with SMA but who do not yet show any symptoms. The study consists of a screening period, a treatment phase, an open-label extension phase of at least 36 months (Month 24 to Month 60) and a follow-up period, for a total treatment duration of at least 5 years for each child included. Children were treated with an oral dose of 0.2 mg/kg risdiplam.

At the time of the interim analysis, a total of 18 patients with presymptomatic SMA were enrolled in RAINBOWFISH. The preliminary effectiveness data for patients with presymptomatic SMA were investigated in 7 patients treated with risdiplam for at least 12 months: Four patients had 2 copies of the SMN2 gene, 2 patients had 3 copies of the SMN2 gene and 1 patient had 4 or more copies of the SMN2 gene. Of these 7 patients, the median age at the first dose was 35 days (range: 16 to 40 days), 71% was female, 100% was white.

The primary endpoint (sitting unsupported for 5 seconds, measured with the *Bayley Scales of Infant and Toddler Development – Third Edition* (BSID III) Gross Motor Scale) was not evaluated. Interim results for the secondary effectiveness endpoints, including the *Hammersmith Infant Neurological Examination, Module 2* (HINE-2), were determined. However, the main objective of this interim evaluation is to evaluate pharmacokinetics and determine the risdiplam dose for patients <2 months.

RAINBOWFISH study outcomes
The 6 patients with 2 or 3 copies of SMN2 achieved the following motor milestones as measured by HINE-2 at 12 months: 6 patients could sit (5 patients could *pivot/rotate* and 1 patient could acquire a stable sitting position), 4 patients

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could stand (3 patients could stand unassisted and 1 patient could stand with support) and 3 patients could walk unassisted. All patients were alive without permanent ventilation after 12 months and were able to receive oral nutrition.

Serious intervention-related adverse effects did not occur and no patient discontinued treatment.

Discussion
Four children with 2 SMN2 copies were treated with risdiplam for 12 months. The probability that a child with 2 SMN2 copies will develop SMA type 1 is 79%. Children with SMA type 1 usually do not reach motor milestones such as rolling over, keeping the head balanced and lifting or sitting unassisted. In the RAINBOWFISH study, these four children could all sit (3 patients could *pivot/rotate* and 1 patient could acquire a stable sitting position). Two of the four children could stand (1 patient assisted and 1 patient unassisted) and one of the four patients could eventually walk unassisted.

Two children with 3 SMN2 copies were also treated with risdiplam for 12 months. The probability that a child with 3 SMN2 copies will develop SMA type 1 or type 2 is 15% and 54%, respectively. Patients with SMA type 2 will still learn to sit, but not stand or walk unassisted. In the RAINBOWFISH study, both children were eventually able to walk unassisted.

From this, we conclude that patients in the RAINBOWFISH study achieve milestones that are usually not achieved by children with 2 or 3 SMN2 copies. In July 2022, based on the mechanism of action, the National Health Care Institute concluded that risdiplam for presymptomatic patients with 2, 3 or 4 copies of SMN2 meets the established medical science and medical practice. The Dutch SMA professional group endorses the view that the most effective treatments are those that are started before any symptoms appear. So far, the interim results of the RAINBOWFISH study confirm this assumption. However, for patients with 3 (and 4) SMN2 copies, a follow-up duration of more than 12 months is required to be more confident about determining whether the presymptomatic patients benefit from risdiplam and perform better than historical control group patients.

Neonates are the most vulnerable subgroup of the paediatric population. Limited safety data are available for this subpopulation with presymptomatic SMA. At a dose of 0.20 mg/kg of risdiplam, the median area under the curve (AUC) was higher than expected. Therefore, a lower dose has been proposed for registration: 0.15 mg/kg of risdiplam for children <2 months of age. Besides, hardly any patients younger than 20 days were treated with risdiplam. The proposed dose of 0.15 mg/kg of risdiplam for neonates younger than 20 days has therefore not been researched. The limited *post-marketing* exposure in countries where the 0.15 mg/kg dose was approved for children aged 0-20 days has so far not produced any safety signals that differ from those previously demonstrated in the population of patients aged 2 months and older. Nevertheless, safety information (including long-term safety) in patients aged <1 month remains very limited. Important potential risks are retinal toxicity and effects on epithelial tissue. The marketing authorisation holder has committed to collect *real world data* from patients with SMA aged < 2 months who are started on risdiplam treatment in the United States. Serious intervention-related adverse effects did not occur and no patient discontinued treatment in the RAINBOWFISH study. Overall, the National

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Health Care Institute concludes, based on interim safety data from a limited number of patients in the RAINBOWFISH study, that the safety profile of risdiplam in presymptomatic patients appears to be consistent with the safety profile of symptomatic patients receiving SMA as an infant and later.

On the basis of the above, it can be concluded that for the assessed indication risdiplam in patients aged between 0 and 2 months meets the established medical science and medical practice.

Farmacotherapeutisch Kompas **advice**
Risdiplam is an orphan drug that is registered for the treatment of 5q SMA, a rare, hereditary, progressive muscle disease. It is effective for patients aged up to 25 years (at the start of treatment) with a clinical diagnosis of SMA type 1, type 2 or type 3 and for presymptomatic patients with 1 to 4 copies of the SMN2 gene. The first results are promising, but there are uncertainties about the effects, especially in the long term. Additional evidence on the benefits and risks of risdiplam is awaited. Given the oral administration, risdiplam appears to be an important addition to the current SMA treatment arsenal consisting of nusinersen (repeated intrathecal injections) and onasemnogene abeparvovec (a single intravenously administered gene therapy).

The efficacy of risdiplam in patients aged > 25 years and a clinical diagnosis of SMA type 2 or type 3 has not (yet) been established.

Budget impact analysis (BIA)
This letter covers the extension of the indication for risdiplam in patients <2 months with symptomatic SMA. A positive advice had already been given for presymptomatic patients <2 months.
In the BIA previously prepared by the National Health Care Institute, the number of incidental and prevalent patients was estimated, including patients <2 months. No distinction was made in patients older and younger than 2 months. Therefore, following the extension of the indication, no more patients are expected to be treated than previously estimated by the National Health Care Institute, since that estimation already included all patients younger than 2 months.

Advice from the National Health Care Institute
The List 2 condition for risdiplam (Evrysdi®) can be extended.

160. Risdiplam
Condition:
Only for insured persons up to and including 25 years old (at the start of treatment):
1. with a clinical diagnosis of 5q SMA type 1, type 2 or type 3, or
2. with a presymptomatic diagnosis of 5q SMA and one to four copies of the SMN2 gene.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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Annex 1: Dosage based on age* and body weight

Age* and body weight	Recommended daily dose
<2 months	0.15 mg/kg
2 months to <2 years	0.20 mg/kg
≥2 years (<20 kg)	0.25 mg/kg
≥2 years (≥20 kg)	5 mg

* Based on corrected age for premature infants