Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
P.O. Box 20350
2500 EJ THE HAGUE

National Health Care Institute Research, Development and Medicinal Products
Medicinal Products Team

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
A. van der Waal
vragen@zinl.nl

Our reference
2026011050

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Date 22 May 2025
Re: Follow-up advice for conditional inclusion of risdiplam (Evrysdi®) for 5q SMA

Dear Ms Hermans,

Based on our advice of 13 August 2025[1], your predecessor identified risdiplam (Evrysdi®) for the treatment of patients aged 26 years and older at the start of treatment with a clinical diagnosis of 5q spinal muscle atrophy (SMA) type 1, type 2 or type 3, or with one to four copies of the SMN2 gene as a potential candidate for conditional inclusion (CI) in the basic health insurance package. It specifically concerns patients who cannot (or can no longer) be treated with nusinersen.

SMA is a rare hereditary muscle disease in which patients become dependent on a wheelchair due to increasing muscular weakness. Ultimately, the muscular weakness leads to curvature of the spine, loss of arm and hand function and paralysis of the respiratory muscles. For SMA patients under 26, risdiplam already meets the criterion of established medical science and medical practice. In the follow-up to our advice, the stakeholders reached an agreement, documented in a covenant, on the data collection linked to CI and on the settlement after the CI period. You have also reached a price arrangement with the marketing authorisation holder.

We have established that all the conditions set out in the CI Framework Letter[2] have been included in the covenant and that all the relevant stakeholders have signed the covenant. We estimate that the agreements made provide sufficient guarantees for the conditional inclusion procedure to proceed carefully and successfully. We assume that, based on the data from the single-centre, single-arm, open-label prospective phase 4 study, at the end of the CI period it is possible to draw a conclusion on the established medical science and medical practice of risdiplam for patients aged over 25 at the start of treatment. We therefore advise you to conditionally include risdiplam in the basic health insurance package for a period of 7 years for the treatment of this specific group of patients.

175 patients are expected to be treated within the CI for risdiplam. Of these,

[1] Advice - risdiplam (Evrysdi®) as a possible candidate for conditional inclusion for the treatment of spinal muscular atrophy (SMA) | National Health Care Institute

[2] Parliamentary paper 29477, no. 621 | Overheid.nl > Official publications

approximately 30 patients have not yet had access to a medicinal product for SMA because they are not eligible for the CI for nusinersen due to contraindications and because they are not eligible for the risdiplam CUP (*Compassionate Use Program*) due to their SMA type 3. The participating treatment centre is the SMA expertise centre at the Utrecht University Medical Center (UMCU).

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After sufficient evidence has been collected for verification on the criterion of the established medical science and medical practice, SWP, the medicinal product either remains in the basic health insurance package after a positive SWP assessment and successful price negotiations for patients over 25, or is removed from the basic health insurance package after a negative SWP assessment or unsuccessful price negotiations for this specific group. The stakeholders have agreed in the covenant that they will comply. In this situation, the reimbursement of risdiplam for this specific group from the basic health insurance package will be discontinued.

The annex provides the explanation behind the advice to conditionally include risdiplam in the basic health insurance package for the treatment of a specific selection of patients with SMA.

If you adopt the advice of the National Health Care Institute, the List 2 condition for risdiplam will need to be amended as follows:

Only
1. for an insured person 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 pre-symptomatic diagnosis of 5q SMA and one to four copies of the SMN2 gene.

Or

2. Pursuant to Article 2.1(5) of the Health Insurance Decision
    Condition:
    Until 01-07-2033 for an insured person with a clinical diagnosis of 5q SMA type 1, type 2 and type 3 aged 26 years or older (at the start of treatment) who cannot (or can no longer) be treated with nusinersen (as assessed by the treatment team of the expertise centre at UMC Utrecht).
    To the extent that the insured party participates in the research referred to in Article 2.2(5).

This adjustment is still pending alignment with the Association of Dutch Healthcare Insurers. If the wording of the List 2 condition is changed, we will inform you.

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

Appendix 1. Explanatory notes on the advice for risdiplam

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The agreed terms and conditions, as mentioned in your Parliamentary Letter on CI of 22 October 2019, are discussed in the covenant[3]. We briefly discuss those elements of the covenant below that are crucial to the success of the conditional inclusion procedure.

The requested intervention includes risdiplam for patients aged 26 and older at the start of treatment with a clinical diagnosis of 5q SMA type 1, 2 and 3, or with one to four copies of the SMN2 gene. It specifically concerns patients who cannot (or can no longer) be treated with nusinersen.

The National Health Care Institute's assessment in July 2022 was that, in the case of patients over 25 years old, there is insufficient evidence to assess whether risdiplam meets established medical science and medical practice (hereinafter also "SWP") for this patient population[4]. The effectiveness of risdiplam had only been studied in patients aged 25 or younger at the start of treatment. Whether risdiplam is also able to slow disease progression and loss of function in patients aged older than 25 at the start of treatment is to be investigated during the CI.

There is currently a CI procedure ongoing for nusinersen (Spinraza®) for patients with 5q SMA aged 9.5 years and older. Nusinersen has a similar mechanism of action to risdiplam. The main difference between the two medicinal products is that risdiplam is available as a powder to make a drink or as a film-coated tablet to be swallowed (oral), whereas nusinersen is available as an injection to be administered via an epidural (intrathecal). Most patients 26 years of age and older who can or could treated with nusinersen are or were participating in the ongoing CI procedure for nusinersen. The request for a CI for risdiplam is thereby restricted to patients who cannot (or can no longer) be treated with nusinersen, because there is an unmet medical need for these patients.

1. *Does the proposed main study address the evidence gap mentioned?*
   During the CI procedure, a single-centre, single-arm, open-label, prospective phase 4 study is carried out on patients aged 26 and older at the start of treatment. Determination of whether risdiplam meets SWP for these patients will be done after the reimbursement decision for nusinersen for the current CI population. The reimbursement decision for nusinersen for the CI population is expected by the end of 2026. The study proposal in the CI request for risdiplam assumes a therapeutic effect comparable to nusinersen, in which the average change in arm function (measured by the Revised Upper Limb Module, RULM) per year during treatment with risdiplam will be compared to the average change in arm function during treatment with nusinersen.

   Two subpopulations are used for the statistical analysis: patients who cannot be given nusinersen and therefore could not participate in the nusinersen CI procedure (the naive subpopulation) and patients who were able to participate in the nusinersen CI procedure but can no longer be treated with that medicinal product (the switchers). The outcomes measured that are crucial for the final assessment by the National Health

[3] Parliamentary paper 29477, no. 621 | Overheid.nl > Official publications

[4] National Health Care Institute. Package recommendation for the lock procedure medicinal product risdiplam (Evrysdi®) in 5q spinal muscular atrophy (SMA). 2022.

Care Institute include mobility and muscle function (RULM), quality of life, severe adverse effects and drop-outs due to adverse effects.

The National Health Care Institute, supported by the Scientific Advisory Board's Medicinal Products Committee (WAR-CG), concludes that a comparison with nusinersen is the highest feasible form of evidence obtainable, even if these patients cannot or can no longer be treated with nusinersen. Based on its therapeutic value being comparable to nusinersen, it is possible to make an indirect assessment of whether risdiplam has added value above the best supportive care in patients who cannot (or can no longer) be treated with nusinersen. A condition for the CI pathway to continue in this form is, however, that nusinersen for patients aged 9.5 and over at the start of treatment does meet SWP in the longer term. The National Health Care Institute has determined that the CI investigation will answer the question posed in the evidence gap.

2. *What difference in effect is considered clinically relevant by the parties involved?*
   There is a clinically relevant effect if a similar value to nusinersen is demonstrated on the critical outcome measures. A clinically relevant effect is at least 0.5 points on the RULM. Since it is not currently known how patients taking nusinersen score on the RULM, once the annual change on the RULM for nusinersen is known, the appropriateness of the 0.5-point non-inferiority limit on the RULM will be reconsidered with the stakeholders. Since little is known in the literature about the clinical relevance limit for quality of life, the National Health Care Institute will assume, if it cannot be established, a standardized mean difference (SMD) of 0.5. As a clinical relevance limit for discontinuation and severe adverse effects, the National Health Care Institute has applied a relative risk (RR) of <0.75 and >1.25.

3. *Will a secondary study be conducted?*
   Since all Dutch patients who cannot (or can no longer) be treated with nusinersen can participate in the main study, no secondary study will be set up in this CI procedure.

4. *Is it clear who will provide the care within the framework of the CI and has the Medical Ethics committee approved the implementation of the secondary study?*
   The covenant states that the study will be carried out by the University Medical Center Utrecht (UMCU). The SMA Centrum Nederland is located at the UMCU. It specialises in the diagnosis, care and treatment of people with SMA. In addition, scientific research on SMA is carried out from the SMA Centrum Nederland.

   The study does not have to meet the WMO (Medical Research Involving Human Subjects Act) conditions. The University Medical Center Utrecht's non-WMO Review Committee has approved the protocol.

5. *Criteria for starting and stopping*
   The treatment team assesses whether a patient cannot (or can no longer) be treated with nusinersen on the basis of pre-defined criteria. Criteria for switching nusinersen may include:
   - Nusinersen injections not possible after spinal fusion (spondylodesis);

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- Administration of nusinersen is no longer possible due to bone formation at the location of the restricted window used for injections;
- Unacceptable burden of injections, for example (but not limited to) need for repeated attempts, severe pain symptoms with fluoroscopy injections;
- The use of nusinersen cannot be continued due to fear of needles or recurrent adverse effects (e.g. severe headache other than due to CSF leakage);
- Other reasons further specified in annual reporting

6. *Are the agreements about monitoring the progress of the study sufficient?*
   The agreement stipulates that the CI period will be 7 years in total. The study itself has an inclusion period of 1.5 years. At the end of the inclusion period there will be a follow-up period of 4 years from the date on which the last patient was enrolled. Following the follow-up period, a period of data analysis and file composition will take place with a maximum duration of 6 months followed by an assessment by the National Health Care Institute and possible price negotiations by the Ministry of Health, Welfare and Sport (VWS) of up to 1 year.

   The National Health Care Institute closely monitors the progress of the research and will report back to you annually. The National Health Care Institute will also use the annual monitoring to assess whether the patients enrolled meet the criteria for not being or no longer being eligible for treatment with nusinersen. If it becomes clear during the CI period that the schedule is not being followed or there are other relevant developments, the National Health Care Institute will inform you and advise you about any adjustment or early termination of the CI if necessary. If nusinersen for patients from the age of 9.5 years at the start of treatment after evaluation by the National Health Care Institute does not comply with the SWP, the study proposal for the CI of risdiplam will need to be updated and reassessed by the National Health Care Institute with the advice of the Scientific Advisory Board (WAR).

7. *Exit criteria and exit strategy*
   A communication plan has been developed describing how patients are informed about the fact that treatment with risdiplam is being temporarily reimbursed as part of a study. If, upon completion of the CI, risdiplam is found to be non-SWP compliant for this particular group of patients, patients will maintain their rights as before the CI. In other words, patients treated within the compassionate use programme (CUP) for risdiplam may continue to be treated with risdiplam without a time limit and as long as treatment is medically indicated. For patients who were not being treated with risdiplam before the CI, treatment will be stopped.

In conclusion, the agreements made give sufficient confidence to start the CI procedure. The National Health Care Institute expects to arrive at clear conclusions about the established medical science and medical practice for patients aged 26 and older at the start of treatment with a clinical diagnosis of 5q SMA type 1, 2 and 3, or with one to four copies of the SMN2 gene within no more than 7 years.

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