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National Health Care Institute
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Our reference
2026001936

Date 26 January 2026
Re: Additional advice on the conditional inclusion of atidarsagene autotemcel (Libmeldy®) for metachromatic leukodystrophy (MLD)

Dear Mr Bruijn,

Based on our advice of 8 May 2023[1], your predecessor identified atidarsagene autotemcel (AA, Libmeldy®), for the treatment of a specific patient group with metachromatic leukodystrophy (MLD), as a potential candidate for conditional inclusion (CI) in the basic health insurance package. This patient group includes early-symptomatic patients with the early juvenile form of MLD who still have the ability to walk independently and before the onset of cognitive decline. For the treatment of pre-symptomatic children with MLD, AA already complies with the established medical science and medical practice. For symptomatic children, there is insufficient evidence whether treatment with AA is effective. In the follow-up to our advice, the stakeholders reached an agreement, documented in a covenant, on the supplementary data collection linked to CI and on the settlement after the CI period. The Minister of Health, Welfare and Sport 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 at the end of the CI period, it will be possible to draw a conclusion about the established medical science and medical practice for AA for this particular group of patients. We will do this on the basis of data from the ongoing international registry study in which Dutch VT patients will also participate. We therefore recommend including AA conditionally in the basic health insurance package for 14 years for the treatment of this specific group of patients.

MLD is an ultra-rare disorder; the submitted application is expected to include just one early-juvenile, early-symptomatic MLD patient in the Netherlands every 3-4 years who could be eligible for AA within the CI period. The participating treatment centres are the Amsterdam University Medical Centre, the University

[1] Advice on a possible candidate for the conditional inclusion of atidarsagene autotemcel (Libmeldy®) | Advice | National Health Care Institute
[2] Parliamentary letter on the policy framework for conditional inclusion of medicinal products | Parliamentary Paper | Rijksoverheid.nl

Medical Centre Utrecht and the Princess Máxima Centre for Paediatric Oncology.

If the National Health Care Institute concludes at the end of the CI period that AA meets the criterion of established medical science and medical practice for this specific patient group, the product will continue to be reimbursed from the basic health insurance package for future patients. If the National Health Care Institute concludes that AA for this specific group does not comply with the established medical science and medical practice, the product may no longer be reimbursed from the basic health insurance package after the end of the CI period for this group. The stakeholders have agreed in the covenant that they will acquiesce. In this situation, the funding of AA for this specific group from the basic health insurance package will be discontinued. Since the gene therapy AA is a one-time treatment, this only affects the consequences for (future) patients who have not been treated with AA during the CI period.

The annex provides the explanation behind the recommendation to conditionally include AA in the basic health insurance package for the treatment of a specific selection of patients with MLD.

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

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Annex 1. Explanation on the advice for atidarsagene autotemcel (AA)

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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 intervention includes atidarsagene autotemcel (AA) for the treatment of metachromatic leukodystrophy (MLD) in early-symptomatic patients with the early juvenile form who can still walk independently and before the onset of cognitive decline. In the initial assessment of AA in 2022, the National Health Care Institute concluded that AA only meets the criterion of established medical science and medical practice for the treatment of pre-symptomatic children with MLD. For symptomatic children, there is insufficient evidence whether treatment with AA is effective. For this population, AA thus does not (yet) meet the established medical science and medical practice.

1. *Does the proposed main study address the evidence gap mentioned?*
   At the time of the initial assessment of AA (2022), the data for early juvenile, early symptomatic patients were very limited; the only data available related to 7 patients with a follow-up of 2-3 years. In addition, 2 out of the 7 early-juvenile, early-symptomatic patients died during follow-up. Based on the baseline characteristics of these two deceased patients, new start criteria for treatment with AA have been established, and the registered indication has been limited. During the CI procedure, it must be demonstrated whether the early-juvenile, early-symptomatic patients deemed eligible for AA based on the current label, will actually benefit from treatment with AA. Longer-term data will also have to be collected (>3 years). There is currently no satisfactory treatment available for this patient population.

   The National Health Care Institute has determined that the international registry study 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 patients have no severe motor impairment for 5 years (Gross Motor Function Classification-Metachromatic Leukodystrophy [GMFC-MLD] <5) and a standardised mean difference of ≥0.5 in cognitive outcomes is achieved (an IQ higher than 55). This is different from the natural course of MLD, suggesting a clinically relevant effect.

3. *Will a secondary study be conducted?*
   Since all Dutch patients 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?*

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

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The covenant states that the participating treatment centres are the Amsterdam University Medical Centre, the University Medical Centre Utrecht and the Princess Máxima Centre for Paediatric Oncology. These are the centres currently treating patients with AA within the indication that already complies with the established medical science and medical practice.

The registry study does not have to meet the WMO (Social Support Act) conditions. The non-WMO Review Committee of the Amsterdam UMC has approved the protocol.

5. *Are the agreements about monitoring the progress of the study sufficient?*
   The covenant sets out the timetable for the registry study within the CI period. The CI period is 14 years. The reporting and analysis of the aggregated data from the *Metachromatic Leukodystrophy Initiative* will be included in the reimbursement file no later than 6 months before the CI period ends and will be presented to the National Health Care Institute by the marketing authorisation holder. 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 how many patients were treated with AA more than 5 years ago. If there is a sufficient number, the National Health Care Institute may decide to introduce a *go/no-go* moment in the interim, whereby the results of the AA treatment from the MLDi registry are indirectly compared with the historical control. Historical control data are derived from a combined cohort of natural history early juvenile (NHx EJ) patients from the natural history study OSR-TIGET and the early symptomatic early juvenile (ES EJ) patients from the MLDi registry. Patients will be matched by age. If it becomes clear during the CI period that patient inclusion is too slow or there are other relevant developments, such as an interim *go/no-go* assessment by the National Health Care Institute, the National Health Care Institute will inform you and advise you on any early termination of the CI if necessary.

6. The communication plan also describes the communication moments and topics.
   As this is a one-time treatment, there are no exit criteria nor an exit strategy. A communication plan has been developed describing how patients are educated about the fact that treatment with AA is being temporarily reimbursed as part of a study.

7. *Criteria for starting and stopping*
   The criteria for starting treatment with the medicinal product are in line with the label criteria. The determination of the indication is independently checked by the appointed indication committee.

In conclusion, the agreements made give sufficient confidence to start the CI procedure. The National Health Care Institute expects to be able to draw clear conclusions on the established medical science and medical practice of AA in the treatment of early-symptomatic MLD patients with the early juvenile form who still have the ability to walk independently and before the onset of cognitive decline, within 14 years at the latest.