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2023015559

Our reference
2023015559

Date 8 May 2023
Re: Advice on a potential candidate for conditional inclusion of atidarsagene autotemcel (Libmeldy®) for metachromatic leukodystrophy MLD) (procedure: orphan drugs, conditionals and exceptionals)

Dear Mr Kuipers,

On 21 February 2023, the applicants submitted an application for the conditional inclusion of orphan drugs, *conditionals* and *exceptionals* for atidarsagene autotemcel (AA, Libmeldy®).

AA is a single-dose gene therapy, registered for the treatment of the rare and hereditary metabolic disorder of metachromatic leukodystrophy (MLD) characterized by bi-allelic mutations in the arylsulfatase A gene (ARSA gene), leading to reduced ARSA enzymatic activity in children with:
- late infantile or early juvenile forms, without clinical manifestations of the disease;
- with the early juvenile form, with early clinical manifestations of the disease, who can still walk independently and before the onset of cognitive decline.

Based on data in the dossier and the advice of the Scientific Advisory Board (WAR), the National Health Care Institute concludes that treatment with AA in the group of patients with the early juvenile form of MLD, with early clinical manifestations of the disease, who are still able to walk independently and before the onset of cognitive decline, meet the criteria for conditional inclusion.

Background
In its advisory report of 27 September 2022, the National Health Care Institute concluded that gene therapy AA can only be reimbursed under conditions for the treatment of children with MLD who do not yet show any symptoms of the disease. Treatment with AA may prevent mental and physical deterioration and eventually death from the disease. For children who already show symptoms of the disease, there is insufficient evidence whether treatment with AA has an effect and therefore, AA does not (yet) meet the established medical science and medical practice. Several parties, including the physicians' association, have indicated that they would also like to have AA available to treat a number of children with minimal symptoms of MLD. The National Health Care Institute therefore assessed, with the applicants, whether AA could become available for

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this group of children through conditional inclusion. A dossier for conditional inclusion was submitted by the marketing authorisation holder in collaboration with the physicians' association and the patients' association on 21 February 2023. The submitted request is related to AA for treatment of children with the early juvenile form of MLD with early clinical manifestations of the disease, who can still walk independently and before the onset of cognitive decline. MLD is an ultra-rare disease; the submitted inclusion is expected to serve only one early juvenile, early symptomatic MLD patient in the Netherlands every 3-4 years who could be eligible for AA within the conditional inclusion procedure.

Disorder and available effectiveness data
MLD is a very serious hereditary metabolic disease in which the storage of certain fats causes the destruction of myelin, which protects the nerve cells. This creates a progressive disease that results in intellectual disability and deterioration of motor skills. The most severely affected patients die from the disease within a few years after the onset of symptoms.

At the time of the initial assessment of AA (2022), the data for early juvenile, early symptomatic patients were very limited; there were only data available from 7 patients with a follow-up of 2-3 years. In addition, 2 of the 7 early juvenile, early symptomatic patients died during the follow-up period. Based on the baseline characteristics of these two deceased patients, new starting criteria for treatment with AA were established and the registered indication was restricted. During the conditional inclusion procedure, it must be demonstrated whether the early juvenile, early symptomatic patients currently labelled eligible for AA will indeed benefit from treatment with AA. Longer-term data will also need to be collected (>3 years). Currently there is no satisfactory treatment available for this patient population.

Study proposal conditional inclusion
Submitting parties have submitted a conditional inclusion study proposal based on an existing multi-centre, multi-national observational registry study (MLDi), which collects both retrospective and prospective data from all MLD phenotypes. Data of early juvenile, early symptomatic patients from different countries treated with AA will be included in the MLDi registry and will be combined with data from patients already treated with AA in the pivotal studies. The efficacy data collected during the CI will be indirectly compared with a combined historical control cohort that receives the best supportive care.

The National Health Care Institute believes that the most uncertainty is regarding the number of patients that will be included in the CI procedure. Due to the ultra-rarity and severity of the disease, the National Health Care Institute considers a registry survey, in which an indirect comparison with a historical control cohort will be made, appropriate in this situation.

Assessment and conclusions
Based on the data in the dossier and the advice of the WAR, the National Health Care Institute has concluded that treatment with AA in early juvenile, early symptomatic MLD patients meets the criteria for the CI[1], namely:

[1] An overview of the criteria for CI can be found in the most recent version of the letter on the conditional inclusion procedure for orphan drugs, conditionals and exceptions. This letter can be found on our website at: https://www.zorginstituutnederland.nl/werkagenda/voorwaardelijke-toelating-weesgeneesmiddelen-

- AA has been granted marketing authorisation by the EMA and has orphan drug status;
- there is an *unmet medical need*;
- The marketing authorisation holder is the dossier's lead applicant. The co-applicants are the treating physicians, an independent research institute and the patients' association;
- Based on the data that will be collected, this registry survey is expected to provide an answer to the package question;
- The National Health Care Institute anticipates that the package question will be answered within 14 years.

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Advice
Based on these conclusions, we recommend that AA (Libmeldy®) should be designated as a potential candidate for conditional inclusion.

Phase 2 of the procedure will commence when you adopt this advice. In this phase, we ask the parties to formulate their plans in greater detail and to draw up a covenant setting out the agreements needed to ensure that the CI process is conducted carefully and successfully. Phase 2 is usually used by the Ministry of Health, Welfare and Sport to reach a financial arrangement with the marketing authorisation holder. In your letter of 12 April 2023 (reference 3571971-1046117-GMT), you inform the Lower House of the Dutch Parliament that negotiations on AA have been conducted with Belgium and Ireland in the context of the Beneluxa collaboration. You describe that no agreement has been reached with the supplier, which means that AA will not be included in the basic health care package. This also means that conditional inclusion for the early symptomatic patients is currently not possible. If the marketing authorisation holder is still willing to agree to an acceptable price and the parties have drawn up a covenant, the National Health Care Institute will prepare an additional advisory report for you to base your final decision about the admission of AA in the conditional inclusion on.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

conditionals-en-exceptionals

Annex 1. Expected patient numbers, price and dose of atidarsagene autotemcel (Libmeldy®)

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Estimated number of patients
Due to the ultra-rarity of the disease, it is difficult to estimate how many Dutch early juvenile, early symptomatic, MLD patients will be treated with AA during the conditional inclusion period. It is expected that 1 early juvenile, early symptomatic MLD patient will be treated with AA every 3-4 years in the Netherlands. Thus, over a period of 14 years, this will be 3-5 patients in total.

Price
AA is a gene therapy with ex vivo genetically modified autologous CD34+ haematopoietic stem and progenitor cells (HSPC). It is a single administration. The dose of Libmeldy to be administered is determined based on the patient's weight at the time of infusion. The minimum recommended dose of Libmeldy is 3 × 106 $CD34^+$ cells/kg. In clinical trials,
doses of up to 30 × 106 $CD34^+$ cells/kg have been administered.[2] AA costs €2,875,000 per patient. The package recommendation for Libmeldy® (National Health Care Institute, September 2022) states that the price should be reduced by 60% for the pre-symptomatic, early juvenile MLD patients (€225,400/QALY) and 85% for the pre-symptomatic, late infantile MLD patients (ICER: €462,632/QALY) to be cost-effective at a reference value of €80,000. It is not described how much the price for the early juvenile, early symptomatic MLD patients has to be reduced in order to be cost-effective. However, an ICER of €396,882/QALY is mentioned for this patient group.[3]

[2] EMA. Summary of Product Characteristics (SmPC): Libmeldy®. 2022.

[3] National Health Care Institute. Packet advice lock procedure medicinal product atidarsagene autotemcel (Libmeldy®). 2022.