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2022034854

Our reference
2022034854

Date 27 September 2022
Subject Package advice lock procedure medicinal product atidarsagene autotemcel (Libmeldy®)

Dear Mr Kuipers,

The National Health Care Institute advises you on atidarsagene autotemcel (AA, Libmeldy®) for the treatment of metachromatic leukodystrophy (MLD). The reason for this advisory report was the placing of the above-mentioned medicinal product in what is known as the 'lock procedure' for expensive medicinal products. The National Health Care Institute carried out the assessment within the 'Beneluxa Initiative' and collaborated with Belgium and Ireland.

AA is an innovative, promising, one-time treatment that addresses the cause of the disease (gene therapy) and it meets the established medical science and medical practice for presymptomatic patients. However, there are uncertainties about the long-term effects: whether the effect truly lasts for life. Furthermore, based on the available data, its cost-effectiveness is uncertain and, as yet, unfavourable.

The National Health Care Institute advises you to include AA in the basic health insurance packagefor presymptomatic patients, provided that a price reduction is achieved and pay-for-performance agreements are made. The Insured Package Advisory Committee (ACP) takes the view that a price above the reference value is socially prudent in this unique case:

- young children who suffer from a very serious condition and who often die young without treatment;
- with a condition that is 'ultra rare' (no more than 2-3 patients per year);
- a treatment with a limited total budget impact.

A pay-for-performance agreement should ensure that the risk of payment for patients who do not respond adequately to the treatment is borne by the manufacturer and not by society. The National Health Care Institute has commissioned Utrecht University to further develop the opportunities for pay for performance for AA. This report is made available to the Office for Financial Arrangement of the Ministry of Health, Welfare and Sport.
In addition, the National Health Care Institute will draw up an orphan drugs arrangement in consultation with the physicians' association and other relevant parties. This arrangement will also take into account the starting criteria. Agreements on the international indication committee and international data

collection and analysis will also be registered in the orphan drugs arrangement.

From various parties, including the physicians' association, we have received signs that they would like AA to be available for some specific early-symptomatic patients. For these patients, the National Health Care Institute cannot conclude, on the basis of the study data, that treatment meets the established medical science and medical practice (because of insufficient data).
For treatments that do not (yet) meet the established medical science and medical practice, the conditional admission (VT) of orphan drugs, conditionals and exceptionals can be applied. The National Health Care Institute is keen to work, with all relevant stakeholders, to see whether this would be an appropriate route to make AA available to a specific group of early-symptomatic patients.

In this letter, I explain our findings and final conclusion.

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General

At your request, the National Health Care Institute assesses whether new care should be part of the basic health insurance package from the perspective of the basic health care package paid from joint premiums. The National Health Care Institute has assessed AA on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. We consider these both in the scientific sense and 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 the established medical science and medical practice, and to determine the cost-effectiveness; and
- the Insured Package Advisory Committee (ACP) for the social deliberations.

We also consulted stakeholders during the assessment process.

Comprehensive weighting of package criteria

Metachromatic Leukodystrophy (MLD) is an autosomal recessive inherited lysosomal storage disorder caused by mutations in the ARSA gene, resulting in a deficient activity of the lysosomal enzyme arylsulfatase A (ARSA), clinically divided into 3 morbidity types, depending on the time of diagnosis:

- late infantile (LI) (≤30 months),
- juvenile (with early juvenile (EJ) 30 months -≤ 7 years and late juvenile 7-≤16 years) and
- adult (age at onset after 16 years).

This is a very serious hereditary metabolic disease in which the storage of certain fats causes the destruction of myeline, 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.

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

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

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

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Established medical science and medical practice
AA treatment is intended as a one-time treatment that should address the underlying genetic cause of MLD. Evidence is based on 2 single-arm studies. One study had a follow-up of 3 years and the other of 1 year. In addition, there is a compassionate use programme (CUP). In total, 12 presymptomatic LI patients have been treated, 5 presymptomatic EJ patients and 7 symptomatic EJ patients. Two of the 7 symptomatic patients have died. In the CUP, 7 presymptomatic LI patients were treated (1 died) and 1 presymptomatic EJ patient (still alive). The GMFM score is the most commonly used outcome measure for measuring the mobility of MLD patients; the IQ score is used for measuring cognitive function. It is expected that AA-treated presymptomatic children have a motor and cognitive progression similar to healthy children, while untreated MLD patients will only suffer deterioration of the disease. The data show that it is important to treat patients before the first symptoms of the disease become visible (presymptomatic). Due to significant short-term effects, which are not or rarely seen in untreated patients with MLD, the Beneluxa assessment team concludes that AA in children with LI or EJ disease types, without clinical manifestations of the disease meets the established medical science and medical practice. For the MLD patients who have been identified as early-symptomatic according to the criteria of the study, there is insufficient data to be able to conclude the established medical science and medical practice.

Budget impact
AA costs €2,875,000 per patient. The cumulative budget impact over three years for the Netherlands is €14,375,000 (based on two patients in year 1, one patient in year 2 and two patients in year 3). The budget impact in the third year is €5,750,000 in the Netherlands.

Cost-effectiveness
The cost-effectiveness analyses of the marketing authorisation holder are of sufficient methodological quality. However, there is some uncertainty about the long-term effects of AA. The review group did not agree with the assumptions made in the model by the marketing authorisation holder and has performed an alternative base case analysis working on the assumption that the treatment effectiveness decreases in some of the patients after 10 years. It is then assumed that after 10 years all complete and stable partial responders also experience reduced motor performance, as is the case for the unstable partial responders. The cost-effectiveness estimates of the review group far exceed the reference value considered relevant to this condition and therefore AA is not a cost-effective intervention. For the presymptomatic LI group, the ICER is €462,632/QALY and for the presymptomatic EJ group, it is €225,400/QALY. At a reference value of €80,000, the price should be lowered by 85% and 60% respectively to be cost-effective.

Orphan drugs arrangement
An orphan drug arrangement will be set up to monitor and track the appropriate use of AA. This will define agreements on the start criteria, an (international) indication committee, data collection and evaluation. The existing MLDi register can be used as a basis.

Final conclusion
The National Health Care Institute advises you to include AA in the basic health insurance packagefor presymptomatic patients, provided that a price reduction is achieved and pay-for-performance agreements are made. The Insured Package Advisory Committee (ACP) takes the view that a price above the reference value is socially prudent in this unique case:

- young children who suffer from a very serious condition and who often die young without treatment;
- with a condition that is 'ultra rare' (no more than 2-3 patients per year);
- a treatment with a limited total budget impact.

A pay-for-performance agreement should ensure that the risk of payment for patients who do not respond adequately to the treatment is borne by the manufacturer and not by society. A research on pay for performance, conducted by Utrecht University, can help with this.
In addition, the National Health Care Institute will draw up an orphan drug arrangement in consultation with the physicians' association and other relevant parties. This arrangement will also take into account the starting criteria. Agreements on the international indication committee and international data collection and analysis will also be registered in the orphan drugs arrangement.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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