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2023048826

Datum 1 december 2023
Betreft update package advice lock procedure medicinal product atidarsagene autotemcel (Libmeldy®)

Onze referentie
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Dear Mr Kuipers,

On request of all Beneluxa partners the National Health Care Institute reviewed new longer term data concerning the medicine atidarsagene autotemcel (AA, Libmeldy®). In a letter from 27 September 2022 the National Health Care Institute advised you on this medicinal product for the treatment of metachromatic leukodystrophy (MLD). The reason for that 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 in 2022 within the 'Beneluxa Initiative' and collaborated with Belgium and Ireland.

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.

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 then available data, its cost-effectiveness was uncertain and, as yet, unfavourable. In 2022 the National Health Care Institute advised you to include AA in the basic health insurance package for presymptomatic patients, provided that a price reduction was achieved and pay-for-performance agreements were made.
Price negotiations between the manufacturer and the Office for Financial Arrangement of your Ministry not resulted in an financial agreement yet. So, in

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The Netherlands AA is still not included in the basic health insurance package. Recently, the manufacturer shared some new (longer term) data with the BeneLuxa partners with the request to review these data and if possible update the conclusions about the cost-effectiveness. This letter will therefore give you an update about our view on the longer term data and the consequences for our previous advise about reimbursement of AA in the Netherlands.

Summary of the assessment and appraisal in 2022

The conclusions of the 2022 assessment of AA were as follows:

- *Effectiveness:* Evidence was based on 2 single-arm studies. One study had a follow-up of 3 years and the other of 1 year. In addition, there was a compassionate use programme (CUP). At that moment in total, 12 presymptomatic LI patients had been treated in the studies, 5 presymptomatic EJ patients and 7 symptomatic EJ patients. In the CUP, 7 presymptomatic LI patients were treated and 1 presymptomatic EJ patient. 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. Due to significant short-term effects, which are not or rarely seen in untreated patients with MLD, the Beneluxa assessment team concluded 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 was 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 was €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 was €5,750,000 in the Netherlands.
- *Cost-effectiveness:* The cost-effectiveness analysis (CEA) and the model of the marketing authorisation holder were of sufficient methodological quality. However, there was 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 review group emphasized that the manufacturers assumption of total cure was very uncertain due to the lack of available data. Implementation of this alternative base case evaluates the maximum impact of this key uncertainty on the cost effectiveness results. The cost-effectiveness estimates of the review group far exceeded the reference value considered relevant to this condition and therefore AA is not a cost-effective intervention. For the presymptomatic LI group, the ICER was €462,632/QALY (ICER manufacturer: €99.035/QALY) and for the presymptomatic EJ group, it was €225,400/QALY (ICER manufacturer: €70.299/QALY). At a reference value of €80,000, the price should be lowered by 85% and 60% respectively to be cost-effective.

  The Insured Package Advisory Committee (ACP) took the view that a price above the reference value was 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.

The National Health Care Institute therefore advised you in 2022 to include AA in the basic health insurance package for presymptomatic patients, provided that a price reduction was achieved and pay-for-performance agreements were made.

Review of new shared long-term data in November 2023

The original assessment of AA was based on data with a data cut off date (DCOD) up to December 2019 from the pivotal trial (201222, NCT01560182). These concerned patients that were treated with the fresh formulation of AA. Only limited data was available on patients using the marketed cryopreserved formulation of AA (from the clinical study 205756 (NCT03392987)). But these last ones were not included in integrated efficacy (pooling data from study 201222, HE 205029, CU 206258, and CU 207394) or the cost-effectiveness analyses presented by the Applicant for HTA.

Updated data in the form of the following separate draft interim clinical study reports (CSR) have been provided by the Applicant in November 2023:

- study 201222 to DCOD March 2022,
- HE 205029 and CU 206258 to DCOD April 2022,
- CU 207394 to DCOD March 2022,
- and study 205756 to DCOD June 2022.
- an updated CSR for the TIGET study with DCOD November 2021.

Updates to the integrated efficacy analyses (pooling data from study 201222, HE 205029, CU 206258, and CU 207394) as provided for HTA have not been provided by the Applicant. Most outcomes data are presented graphically in the CSRs, without additional statistical analyses.

Based on the new data the Review Group has summarised changes in these outcomes relative to data provided during the original assessment. The median duration of post-treatment follow-up from the pivotal trial (study 201222) was 9.52 years (range 6.52 to 11.03 years) in the treated LI subjects and 7.46 years (range 0.64 to 10.61 years) in treated EJ subjects in the updated data. Duration of follow up from the HE/CU programs is shorter. Therefore, data to 10 years is only available for a small proportion of AA treated patients (n=5) and the longer-term effectiveness of AA remains uncertain.

Outcomes for the AA treated PS LI patients (study 201222, HE205029 and CU 206258 in updated data (n=15))

Follow-up 10 years or longer: From the four patients with a follow up of 10 years or longer one full responder patient seemed to be stable and still categorized as a full responder after 10 years. One partial stable responder remained stable on mobility but worsened a little on cognitive impairment (from no cognitive impairment to mild impairment). Two other full responders experienced a little in motor function 10 years after AA treatment (from GMFC-MLD stadium 0 to 1) and their cognitive impairment worsened a bit (from none cognitive impairment to moderate impairment).

Follow-up 8 to 10 years: Both patients (one partial stable responder and one unstable responder) experienced a little decline in motor function.

Follow-up 6 to 8 years: one full responder remained stable and experienced no decline in motor function and cognitive impairment.

Follow-up 4 to 6 years: two full responders remained stable and experienced no

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decline in motor function and cognitive impairment. Five partial stable responders remained stable and experienced no decline in motor function and cognitive impairment. Two of them seemed to experience an increase on GMFC-MLD score (one patient from 1 to 0 and the other from 2 to 1).

Outcomes for the AA treated PS EJ patients (study 201222 and CU 206258 in updated data (n=5))
Follow-up 8 to 10 years: one full responder remained stable and experienced no decline. Another full responder experienced a little decline in motor function from GMFC-MLD score 0 to 1. Both patients experienced no cognitive impairments.
Follow-up 6 to 8 years: One full responder remained stable and experienced no decline in motor function or cognitive impairment. One partial stable responder worsened in motor function (from GMFC-MLD score 2 to 4). For this patient no data are available about the cognitive impairment.

Conclusion and advise of the National Health Care Institute
From the longer term data it can be concluded that there are AA treated patients that remain stable after longer follow-up. Within these patients it looks as if the effect of AA treatment remains and no decline in effect had been experienced. On the other hand it can be seen from the longer-term data that some patients show a worsening in treatment effect. We want to emphasize that these data are based on small patient numbers because not many patients have reached a follow-up longer than 8 years yet.
Based on these new data we still think that the manufacturers assumption about the life long effect for full responders and partial responders is too optimistic. The alternative ICER as previously estimated by the review group was a maximum estimate. The assumption was that 10 years after treatment the full and partial responders followed the same decline as the unstable responders. From the recent delivered data this assumption seems not realistic neither.
Based on the previous mentioned data we conclude that the cost-effectiveness of AA for the treatment of presymptomatic LI patients is between €99.035/QALY (ICER manufacturer) and €462,632/QALY (ICER review group in 2022). The cost-effectiveness of AA for the treatment of presymptomatic EJ patients is between €70.299/QALY (ICER manufacturer) and €225,400/QALY (ICER review group in 2022).
The National Health Care Institute advises you, based on the insights from the newly provided longer term data, to start new price negotiations for AA. The uncertainty about the long term effectiveness remains but decreases based on the new data. Therefore, it is expected that the cost-effectiveness is more favorable than initially estimated by the review group. The necessary price reduction will therefore be lower than mentioned in our earlier advice. Although we still think the manufacturers scenario (0% price reduction) is not realistic, we think that looking at the additional longer term data that the required price reduction is lower than the initially advised 60-85%. Based on these new insights we advise you to restart new price negotiations for AA, by including this new information.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

CC: