Rare disease
Sector: Hospital

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 APRIL 2021

The legally binding text is the original French opinion version

Autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene
LIBMELDY, 2-10 x 10^6 cells/mL dispersion for infusion

First assessment

Key points

Favourable opinion for reimbursement in the treatment of metachromatic leukodystrophy (MLD) only in asymptomatic children without clinical manifestations of the disease in terms of motor, cognitive and/or behavioural functional impairment, with late infantile (onset before 30 months of age) or early juvenile (onset from 30 months to 6 years of age inclusive) forms.

Unfavourable opinion for reimbursement in the treatment of metachromatic leukodystrophy (MLD) in symptomatic children with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline, with the early juvenile form (onset from 30 months to 6 years of age inclusive).

What therapeutic improvement?

Therapeutic improvement in the management of metachromatic leukodystrophy (MLD) in asymptomatic children with late infantile (onset before 30 months of age) or early juvenile (onset from 30 months to 6 years of age inclusive) forms.

◗ Role in the care pathway?

The care pathway for metachromatic leukodystrophy (MLD) is currently based on symptomatic treatment.

Allogeneic haematopoietic stem cell transplantation (HSCT) is a currently available alternative to correct the enzyme deficiency, generally reserved for milder forms of MLD corresponding to the juvenile and adult forms. Current results for the efficacy of allogeneic HSCT in patients with juvenile forms are heterogeneous, however, and relate to small patient cohorts or case studies. It has been suggested that transplantation would have more impact in the event of early use, at the very start of the disease rather than at an advanced stage. However, allogeneic grafts are ineffective to prevent progression of the disease in aggressive forms, such as late infantile forms or early forms with evident neurological symptoms; that is because the rapid progression of the disease at these stages is incompatible with the very gradual nervous system microglia and macrophage replacement time associated with central reconstitution of arylsulfatase A (ARSA) enzymatic activity following transplantation.

Finally, phase 1/2 and 2 trials are currently ongoing with the following new treatment methods, being investigated in MLD:

- enzyme replacement therapy, with the administration of human recombinant ARSA by intravenous or intrathecal injections;
- gene therapy:
  - direct intracerebral administration of adeno-associated viral vector.
  - direct intracerebral administration of lentiviral vector.
  - administration of autologous CD34+ cells transduced ex vivo using a lentiviral vector encoding the ARSA/ABCD1 gene, including the product assessed in this opinion.

Role of the medicinal product in the care pathway

Considering:

- **the observed efficacy:**

• in terms of motricity on the GMFM score after 2 years, with a difference of 65.1% in asymptomatic patients with the infantile form (onset before 30 months of age) and 52.4% in asymptomatic patients with the early juvenile form (onset from 30 months to 6 years of age inclusive) compared to the natural history cohort,

• on the observed increase in ARSA activity after 2 years (second co-primary efficacy endpoint):

- with an activity multiplied by 8.6 (CI95% = [3.9; 19.2]) in children with a late infantile form,

- with an activity multiplied by 7.3 (CI95% = [3.6; 14.9]) in children with an early juvenile form

• on cognitive function, assessed using IQ scales in asymptomatic patients with the late infantile form (onset before 30 months of age) or early juvenile form (onset from 30 months to 6 years of age inclusive),

• but with less benefit in symptomatic children with the early juvenile form.

- **limited short-term safety data with signals relative to immunisation, and the important potential risk identified in the RMP on malignancy associated with insertional mutagenesis,**
- **limitations related to the manufacturing and administration circuit with, in particular, adverse events related to busulfan conditioning,**

LIBMELDY is a therapeutic option in metachromatic leukodystrophy (MLD) only in asymptomatic children without clinical manifestations of the disease in terms of motor, cognitive and/or behavioural functional impairment, with late infantile (onset before 30 months of age) or early juvenile (onset from 30 months to 6 years of age inclusive) forms.

In the other children covered by the scope of the MA for LIBMELDY corresponding to the treatment of metachromatic leukodystrophy (MLD) in symptomatic children with early clinical manifestations of the disease who still have the ability to walk independently and before the onset of cognitive decline, with the early juvenile form (onset from 30 months to 6 years of age inclusive), the Committee considers that LIBMELDY has no role in the care pathway.

The Summary of Product Characteristics (SPC) and the Risk Management Plan (RMP) must be complied with. Special monitoring during and after treatment is required.

According to the SPC, patients should undergo regular monitoring of anti-ARSA antibodies (AAA) before treatment and for up to 15 years post-treatment. The theoretical risk of leukaemia or lymphoma after treatment with LIBMELDY should also be monitored.

Special recommendations

The Committee highlights the benefit to patients and their carers of having access to appropriate information on the complexity of the gene therapy procedure and the risks to patients, in particular:

- the uncertainties relative to maintenance of efficacy in the medium and long term,
- the uncertainties relative to safety, including the potential risk of immunisation and insertional mutagenesis in a context in which the median duration of follow-up after LIBMELDY treatment is 4.5 years on a limited patient population,
- the impact on fertility of LIBMELDY treatment, related to administration of busulfan during the conditioning phase.

Considering the complexity of the gene therapy procedure with LIBMELDY, its use strictly limited to a small population of patients with MLD and uncertainties in terms of the maintenance of its efficacy and its long-term safety:

- The decision to treat a patient with LIBMELDY should be discussed at a multidisciplinary team (MDT) meeting attended by professionals from a reference centre experienced in allogeneic bone marrow transplantation and gene therapy in metachromatic leukodystrophy.
- The prescription of LIBMELDY and its administration should be reserved for qualified reference centres, by physicians experienced in HCST and in the treatment of metachromatic leukodystrophy, in accordance with the requirements of the SPC and according to expert opinion.

In this context, the Committee highlights the importance of overall care (in particular including travel and local accommodation near healthcare facilities, where required).

The Committee will reassess LIBMELDY within a maximum period of 3 years, on the basis of the data requested, including the interim analyses of studies not completed on this date.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Metachromatic leukodystrophy (MLD) is a serious, rare and fatal disease, with the late infantile form (onset before 30 months of age) being the most aggressive.

◗ The proprietary medicinal product LIBMELDY (Autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene) is a curative medicinal product.

◗ Considering data demonstrating:

- an improvement in the GMFM motor score after 2 years compared to the natural history of the disease, considered to be clinically relevant, of:
  - + 65.1% for 9 asymptomatic children with a late infantile form (onset before 30 months of age),
  - + 52.4% for 4 asymptomatic children with an early juvenile form (onset from 30 months to 6 years of age inclusive),
- a suggested lesser benefit in terms of improvement in the GMFM motor score after 2 years compared to the natural history of the disease for 7 symptomatic children with an early juvenile form (onset from 30 months to 6 years of age inclusive) (observed difference of + 28.7%) and for whom the motor deterioration was more rapid than that of asymptomatic patients (mean GMFM score after 2 years of 96.7% for asymptomatic children and 60.7% for symptomatic patients treated with LIBMELDY).
- An observed increase in ARSA activity after 2 years (second co-primary efficacy endpoint):
  - with an activity multiplied by 8.6 (CI95% = [3.9; 19.2]) in children with a late infantile form,
  - an activity multiplied by 7.3 (CI95% = [3.6; 14.9]) in children with an early juvenile form
- a short-term safety profile (median follow-up duration of 4.5 years (min-max: 0.6 - 9 years)) with signals relative to immunisation, and the important potential risk identified in the RMP on malignancy associated with insertional mutagenesis,
- and in view of the burden of conditioning in terms of management and adverse events,

The efficacy/adverse effects ratio is **high in the short term** in **asymptomatic** children with a late infantile form (onset before 30 months of age) or early juvenile form (onset from 30 months to 6 years of age) of metachromatic leukodystrophy.
The efficacy/adverse effects ratio has **not been adequately established** in children with an early juvenile form **(onset from 30 months to 6 years of age inclusive)** of metachromatic leukodystrophy **with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline**.

◗ For asymptomatic late infantile forms, there are no therapeutic alternatives in the treatment of metachromatic leukodystrophy.
For early juvenile forms of metachromatic leukodystrophy, allogeneic transplantation is a therapeutic alternative in the event of administration at an early stage of the disease when symptoms have not yet developed or immediately following the onset of the first symptoms (see section 5.2 Clinically relevant comparators).

In the treatment of metachromatic leukodystrophy (MLD) in asymptomatic children without clinical manifestations of the disease in terms of motor, cognitive and/or behavioural functional impairment, with late infantile (onset before 30 months of age) or early juvenile (onset from 30 months to 6 years of age inclusive) forms: LIBMELDY is a therapeutic option.

In the other children covered by the scope of the MA for LIBMELDY corresponding to the treatment of metachromatic leukodystrophy (MLD) in symptomatic children with early clinical manifestations of the disease who still have the ability to walk independently and before the onset of cognitive decline, with the early juvenile form (onset from 30 months to 6 years of age inclusive): LIBMELDY has no role in the care pathway.

Public health impact

Considering:

- the seriousness of this rare, fatal disease, for which the prevalence in Europe is estimated to be 0.1/100,000[Erreur ! Signet non défini.] and the incidence to be 1.47 out of every 100,000 live births;
- the identified medical need;
- the partial response to the identified need in terms of motor function, cognitive function and survival in asymptomatic children with the late infantile or early juvenile forms of the disease;
- the expected additional impact of LIBMELDY on morbidity and mortality, with modification of the natural course of the disease in asymptomatic forms, but not yet demonstrated in the long term based on the available data. The impact on quality of life cannot be assessed in the absence of available data;
- with a transposability that is not guaranteed given the small number of patients included in a single Italian centre;
- uncertainties relative to the maintenance of patient eligibility between the initial visit and transplantation in the event of rapid disease progression;
- the impact on the care and life pathway for patients and their families, and on the organisation of care, with:
    - initial management in a qualified haematopoietic stem cell transplant centre,
    - transplant conditioning with busulfan, with expected adverse effects,
    - hospitalisation of patients far from home, for a duration of several weeks,

LIBMELDY is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of LIBMELDY (Autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene) is:

- **substantial in the treatment of metachromatic leukodystrophy (MLD) only in asymptomatic children without clinical manifestations of the disease in terms of motor, cognitive and/or behavioural functional impairment, with late infantile (onset before 30 months of age) or early juvenile (onset from 30 months to 6 years of age inclusive) forms.**
- **insufficient to justify its public funding cover in the other children covered by the scope of the MA for corresponding to the treatment of metachromatic leukodystrophy (MLD) in symptomatic children with early clinical manifestations of the disease who still have the ability to walk independently and before the onset of cognitive decline, with the early juvenile form (onset from 30 months to 6 years of age inclusive).**

The Committee issues:

- **a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of metachromatic leukodystrophy (MLD) only in asymptomatic children without clinical manifestations of the disease in terms of motor, cognitive and/or behavioural functional impairment, with late infantile (onset before 30 months of age) or early juvenile (onset from 30 months to 6 years of age inclusive) forms.**
- **an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the other children covered by the scope of the MA corresponding to the treatment of metachromatic leukodystrophy (MLD) in symptomatic children with early clinical manifestations of the disease who still have the ability to walk independently and before the onset of cognitive decline, with the early juvenile form (onset from 30 months to 6 years of age inclusive).**

Clinical Added Value

Considering:

- **results considered to be clinically relevant demonstrating the efficacy of LIBMELDY on the total GMFM score after 2 years (co-primary efficacy endpoint) only in asymptomatic children (exploratory subgroups), with a difference of 65.1% in asymptomatic children with the infantile form (n=9) and 52.4% in asymptomatic patients with the early juvenile form (n=4) compared to the natural history cohort, assessed during a phase 1/2 single-centre comparative study versus a historic cohort of 31 patients,**
- **the observed increase in ARSA activity after 2 years (second co-primary efficacy endpoint):**
    - **with an activity multiplied by 8.6 (CI95% = [3.9; 19.2]) in children with a late infantile form,**
    - **an activity multiplied by 7.3 (CI95% = [3.6; 14.9]) in children with an early juvenile form**
- **the absence of observed deterioration in terms of cognitive functions on the IQ scale for these same patients (exploratory secondary endpoint of the study), but**
- **numerous uncertainties, concerning in particular:**
    - **the maintenance of medium and long-term efficacy in view of the maximum follow-up of LIBMELDY treatment currently limited to a median of 4.5 years for a limited number of patients,**
    - **the long-term safety of LIBMELDY, particularly in view of the potential risk identified in the RMP on malignancy associated with insertional mutagenesis and signals relative to immunisation,**
    - **the absence of robust data on quality of life for patients and their carers,**

the Committee considers that LIBMELDY provides a moderate clinical added value (CAV III) in the treatment of metachromatic leukodystrophy (MLD) in asymptomatic children without clinical manifestations of the disease in terms of motor, cognitive and/or behavioural functional impairment, with late infantile (onset before 30 months of age) or early juvenile (onset from 30 months to 6 years of age inclusive) forms.

According to Orphanet[Erreur ! Signet non défini.] data, the prevalence of metachromatic leukodystrophy is estimated to be 1.47/100,000 births, i.e., 10 children.
Since the late infantile form represents 40 to 60%[Erreur ! Signet non défini.] of patients (i.e., 4 to 6 children) and the early juvenile form represents 20 to 40%[Erreur ! Signet non défini.] of patients (i.e., 2 to 4 children), the number of patients concerned by the LIBMELDY indication is estimated to be between 6 and 10 children per year.
According to expert opinion, the target population of asymptomatic patients liable to benefit from LIBMELDY is around 3 children.

In total, the target population of LIBMELDY is estimated to be a maximum of around 3 children per year.