SUMMARY

atidarsagene autotemcel

LIBMELDY, 2-10 x 10^6 cells/mL

dispersion for infusion

First listing

Adopted by the Transparency Committee on 6 November 2024

Summary of opinion

Favourable opinion for maintenance of reimbursement in the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:

- **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 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).**

Transparency Committee's conclusions

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 (atidarsagene autotemcel) is a curative medicinal product.
- The efficacy/adverse effects ratio is **high in the short term** in the treatment of metachromatic leukodystrophy (MLD) characterised by biallelic mutations in the arylsulfatase A gene leading to a reduction of the ARSA enzymatic activity:
  - 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 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).
- This is a first-line treatment in the absence of available therapies.

➔ Public health benefit

Considering:

- the seriousness of this rare, fatal disease, for which the prevalence in Europe is estimated to be 0.1/100,000 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, without clinical manifestations of the disease, with the late infantile or early juvenile forms of the disease and in symptomatic children with early clinical manifestations of the disease with the early juvenile form of the disease, given:
  - the additional impact of LIBMELDY observed 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 additional impact of LIBMELDY (atidarsagene autotemcel) observed on morbidity with an effect size that appears to be lower in the subpopulation of symptomatic patients, with early clinical manifestations of the disease, with the early juvenile form (onset from 30 months to 6 years of age inclusive) (exploratory subgroup), and without any effect on mortality in this subgroup,
  - the lack of evidence of an impact on quality of life in the absence of relevant data,
- uncertainties with respect to the transposability of the results 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 (atidarsagene autotemcel) is unlikely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the clinical benefit of LIBMELDY (atidarsagene autotemcel) is substantial in the MA indications.

The Committee issues a favourable opinion for inclusion of LIBMELDY (atidarsagene autotemcel) in the list of covered drugs for inpatients approved for use in the MA indications and at the MA dosages.

Clinical Added Value

Considering:

- the results of a single-centre phase 1/2 study demonstrating the efficacy of LIBMELDY on the total GMFM (Gross Motor Function Measure) score after 2 years (co-primary efficacy endpoint) compared to a matched natural history cohort of 41 patients with a size effect considered to be clinically relevant:
  - in **asymptomatic** children (exploratory subgroups) with a difference of 65.4% in children with the late infantile form (n = 9) and 46.1% in children with the early juvenile form (n = 4)
  - in **symptomatic** children (exploratory subgroup) with the early juvenile form (n=7) with a lower difference of 20.1%,
- the observed increase in ARSA activity after 2 years compared to inclusion (second co-primary efficacy endpoint):
  - with an activity multiplied by 8.6 ($CI_{95\%}$= [3.9; 19.2]) in children with the late infantile form,
  - with an activity multiplied by 7.3 ($CI_{95\%}$ = [3.6; 14.9]) in children with the early juvenile form,
- the absence of observed deterioration in terms of cognitive functions on the IQ scale (exploratory secondary endpoint of the study) at the end of follow-up:
  - for 6/9 and 7/9 children with the late infantile form, respectively, on the performance (IQ ≥ 70) and verbal (IQ > 55) scores
  - for 6/11 children with the early juvenile form, respectively, on the performance (IQ ≥ 85) and verbal (IQ ≥ 70) scores,
- the unmet medical need in these populations,

but taking into account numerous uncertainties, concerning in particular:

- the methodological limitations associated with this study (single-centre, small population size, analysis in exploratory subgroups, non-exact matching based on only two patient characteristics associated with difference in characteristics at baseline compared to the historic cohort), potentially leading to bias in the estimation of the real effect size of the treatment, particularly in each of the subpopulations concerned,
- maintenance of efficacy in the long term in view of the currently limited maximum treatment follow-up (median follow-up of 9.5 years in children with the late infantile form and 7.5 years in children with the early juvenile form), for a limited number of patients,
- the long-term safety, particularly in view of the high potential risk identified in the RMP on malignancy associated with insertional oncogenesis and signals relative to immunisation,
- the absence of robust data on quality of life for patients and their carers,

the Committee considers that LIBMELDY (atidarsagene autotemcel) 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
- a minor clinical added value **(CAV IV) 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).