Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Atidarsagen autotemcel (metachromatic leukodystrophy with biallelic mutation in the ARSA gene)

of 4 November 2021

At its session on 4 November 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient atidarsagen autotemcel as follows:

Atidarsagen autotemcel

Resolution of: 4 November 2021
Entry into force on: 4 November 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 17 December 2020):

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 children with late infantile or early juvenile forms, without clinical manifestations of the disease; in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

Therapeutic indication of the resolution (resolution of 4 November 2021):

see therapeutic indication according to marketing authorisation

1. Extent of the additional benefit and significance of the evidence

Atidarsagen autotemcel (OTL-200) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

a) Children with late infantile (LI) or early juvenile (EJ) forms of metachromatic leukodystrophy (MLD) without clinical manifestations of the disease

   Extent of the additional benefit and significance of the evidence of atidarsagen autotemcel:

   Hint of a major additional benefit

b) Children with the EJ form of metachromatic leukodystrophy with early clinical manifestations of the disease who still have the ability to walk independently, before the onset of cognitive decline

Extent of the additional benefit and significance of the evidence of atidarsagen autotemcel:

Hint for a non-quantifiable additional benefit, since the scientific data does not allow a quantification.

Study results according to endpoints: [1]

a) Children with late infantile (LI) or early juvenile (EJ) forms of metachromatic leukodystrophy (MLD) without clinical manifestations of the disease

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↑	Advantages in motor development (GMFM)
Health-related quality of life	∅	No data available.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

Study results of the sibling analysis from the integrated dataset (IDS) of the marketing authorisation studies and their historical control of the natural history cohort (TIGET Nhx study).

[1] Data from the dossier assessment of the G-BA (published on 2 August 2021 and the amendments (published on 4 November 2021)

Mortality

	Intervention (OTL-200) N = 12	**Natural history cohort (TIGET-NHx)** N = 11
Sibling analysis[i)]		
Death, n (%)	0 (0)	4 (36)
Observation duration (in months), median [95% CI]	n.d.	n.d.
Survival time (in years), Median [95% CI]	n. c. [n. c.; n. c.]	n. c. [5.7; n.a.][a)]
Hazard ratio [95% CI], p-value[a)b)]		-[c)], 0.024

Morbidity

	Intervention (OTL-200) N = 12	**Natural history cohort (TIGET-NHx)** N = 11
Sibling analysis[i)]		
Motor development: GMFM (Gross Motor Function Measure)		
Total at baseline[f)] in %, n (%) Mean value (SD) Median (min; max)	12 (100) 71.5 (19.9) 75.3 (27.3; 98.6)	11 (100) 14.5 (19.4) 5.9 (1.2; 61.2)
Total at year 2[g)] in %, n (%) Mean value (SD) LS mean [95% CI][h)b)]	10 (83) 80.30 (26.999) 80.03 [64.47; 95.588]	9 (82) 28.49 (32.165) 28.79 [12.39; 45.184]
LS MD [95% CI]; p-value[h)b)]	51.25 [28.644; 73.846], 0.0002	
Total at year 3[g)] in %, n (%) Mean value (SD) LS mean [95% CI][h)g)]	11 (92) 80.77 (27.483) 81.31 [67.798; 94.831]	10 (91) 9.49 (14.567) 8.89 [-5.287; 23.070]
LS MD [95% CI]; p-value[h)b)]	72.42 [52.808; 92.038], <0.0001	

	Intervention (OTL-200) N = 12	Natural history cohort (TIGET-NHx) N = 11
Sibling analysis[i)]		
Presented additionally: **Gross motor functions: GMFC (Gross Motor Function Classification)-MLD level**		
GMFC-MLD level ≥ 5, n (%)	1 (8)	11 (100)
Observation duration (in months), median [95% CI]	n.d.	n.d.
Age (in years), Median [95% CI]	n.c. [n.c.; n.c.]	3.60 [2.90; n.c.]
Hazard ratio [95% CI][d)], p-value [a)e)]	0.15 [0.019; 1.152], 0.035	

a) p-value from log-rank test
b) calculated post hoc
c) No event occurred in the intervention arm of the comparison (OTL-200) during the observation period. Therefore, no adequate hazard ratio can be determined.
d) Hazard ratio and 95% CI Cox regression with categorical covariate treatment.
e) Hazard ratio, 95% CI and p-value: calculated post hoc.
f) Baseline refers to the time of the first measurement at the start of the study in the OTL-200 arm and to the time of the baseline visit in the TIGET NHx study. To the extent that no baseline value was available for patients in the TIGET NHx study at the time of enrolment, values at the time of the most recent survey that could be recorded retrospectively were used.
g) Includes measurement at the time of visit 2 or 3 years after OTL-200 administration in the OTL-200 arm and measurement from visits of "matched" children in the TIGET-NHx arm.
h) Designated by the pharmaceutical company as a linear model, adjusted for age. In module 4, one-way testing using ANCOVA and a linear model are mentioned. The statement describes a linear model with an analogous model structure to the ANCOVA in the EPAR. The EPAR mentions a two-way test.
i) Matched Sibling Analysis Set (MSAS): includes all patients in the ITT population with a sibling in the TIGET NHx study and all siblings in the TIGET NHx study.

Abbreviations:
CUP: Compassionate Use Program; GMFC-MLD: Gross Motor Function Classification in MLD; GMFM: Gross Motor Function Measure; HE: Hospital Exemption; IDS: Integrated Dataset; CI: Confidence Interval; LS: Least Squares; max.: Maximum value; MD: Mean difference; min: Minimum value; MLD: Metachromatic Leukodystrophy; MSAS: Matched Sibling Analysis Set; n. c.: not calculable; SD: Standard Deviation; TIGET-NHx: Telethon Institute for Gene Therapy Natural History

Health-related quality of life

No endpoints from quality of life category were assessed.

Side effects[2]

Summary of the AE	**Intervention (OTL-200)** Start of study until conditioning (Day -5)[b)] N = 29	**Intervention (OTL-200)** From start of conditioning (Day -4) to data cut-off[c)] N = 29[d)]
Integrated Dataset (IDS)		
Subjects with at least one:		
AE, n (%)	29 (100)	29 (100)
AE CTCAE grade ≥ 3, n (%)	7 (24)	29 (100)
SAE, n (%)	2 (7)	20 (69)
AE that led to therapy discontinuation	n. d.[e)]	n. d.[e)]

a) All included patients who received OTL-200.
b) Period from the day of signing the consent form until the day before the start of conditioning with busulfan.
c) Data cut-offs dated 30.03.2018 (study 201222), 05.01.2018 (CUP 207394) and 05.12.2018 (CUP 206258 and HE 205029).
d) Data from module 4.
e) The approach of the pharmaceutical company to equate the occurrence of a death with an AE that led to therapy discontinuation is not followed. The occurrence of AE may result in not starting conditioning or not administering the OTL-200 infusion after conditioning. The pharmaceutical company does not present these therapy discontinuations due to AEs.

Abbreviations:
CTCAE: Common Terminology Criteria for Adverse Events; IDS: Integrated Dataset; n.d. = no data ; pU: pharmaceutical company; (S)AE: (serious) Adverse Event

[2] No safety data are available for children from the historical control on natural history (TIGET-NHx).

b) Children with the EJ form of metachromatic leukodystrophy with early clinical manifestations of the disease who still have the ability to walk independently, before the onset of cognitive decline

The data are not assessable.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	∅	No data available
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

2. Number of patients or demarcation of patient groups eligible for treatment

a) Children with late infantile (LI) or early juvenile (EJ) forms of metachromatic leukodystrophy (MLD) without clinical manifestations of the disease.

b) Children with the EJ form of metachromatic leukodystrophy with early clinical manifestations of the disease who still have the ability to walk independently, before the onset of cognitive decline

approx. 1 – 3 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Libmeldy (active ingredient: atidarsagen autotemcel) at the following publicly accessible link (last access: 28 October 2021):

https://www.ema.europa.eu/en/documents/product-information/libmeldy-epar-product-information_en.pdf

Treatment with atidarsagen autotemcel should only be initiated and monitored by medical staff experienced in hematopoietic stem cell transplantation.

Libmeldy must be administered in a qualified treatment centre with experience in hematopoietic stem cell transplantation (HSCT). Patients are expected to participate in a long-term follow-up study to better understand the long-term safety and efficacy of Libmeldy.

4. Treatment costs

Treatment costs:

a) Children with late infantile (LI) or early juvenile (EJ) forms of metachromatic leukodystrophy (MLD) without clinical manifestations of the disease

Designation of the therapy	Treatment costs/ patient
Medicinal product to be assessed:	
Atidarsagen autotemcel[3,4,5]	€ 2,875,000
additionally required SHI services	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2021)

b) Children with the EJ form of metachromatic leukodystrophy with early clinical manifestations of the disease who still have the ability to walk independently, before the onset of cognitive decline

Designation of the therapy	Treatment costs/ patient
Medicinal product to be assessed:	

[3] Single dose
[4] It concerns only the cost of the medicinal product.
[5] Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 of the German Medicines Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed..

Designation of the therapy	Treatment costs/ patient
Atidarsagen autotemcel[6,7,8]	€ 2,875,000
additionally required SHI services	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2021)

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 4 November 2021.**

2. **The period of validity of the resolution is limited to 1 July 2024.**

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 4 November 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

[6] Single dose
[7] It concerns only the cost of the medicinal product.
[8] Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 of the German Medicines Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.