Gemeinsamer Bundesausschuss

Justification

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

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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence 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. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB

V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing of the active ingredient atidarsagen autotemcel on the (German) market in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 May 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 April 2021.

Atidarsagen autotemcel for the treatment of metachromatic leukodystrophy is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 02 August 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G21-16) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the G-BA.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of atidarsagen autotemcel.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of atidarsagen autotemcel (Libmeldy) in accordance with the product information

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 the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

The marketing authorisation population includes children with EJ (Early Juvenile) form with early clinical manifestations of the disease but who still have the ability to walk independently, before the onset of cognitive decline, as well as children with Late Infantile (LI) or EarlyJuvenile (EJ) forms of metachromatic leukodystrophy (MLD) without clinical manifestations of the disease. As the children in the population relevant for the benefit assessment differ with regard to existing symptoms and the manifestation of the disease, two patient groups are distinguished with regard to the assessment of the additional benefit.

In summary, the additional benefit of atidarsagen autotemcel is assessed as follows:

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

   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

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

Justification:

Aspects across patient groups for the benefit assessment

Atidarsagen autotemcel (hereinafter OTL-200) is an ATMP (advanced therapy medicinal product) containing a population of hematopoietic stem and progenitor cells (HSPC), enriched with autologous CD34+ cells, transduced *ex vivo* using a lentiviral vector, encoding the gene for human arylsulfatase A (ARSA).

Results from an integrated dataset (IDS), including the four marketing authorisation studies 201222, Compassionate Use Program (CUP) 207394, CUP 206258, and Hospital Exemption (HE) 205029 are available to assess the extent of additional benefit of OTL-200 compared to a legacy control of natural history of the disease (TIGET NHx study). All four studies were conducted at the same treatment centre.

The natural history cohort included children with a form of MLD occurring in late infancy (LI) or MLD occurring in early childhood (EJ). Children were included in the natural history cohort who were not eligible for participation in the four marketing authorisation studies due to their advanced stage of disease but who received treatment at the same treatment centre.

The mean age at the time of enrolment in the OTL-200 arm was 41.5 months, while children in the natural history cohort were significantly older on average at 102.2 months. In the mean GMFM (Gross Motor Function Measure) score, children from the natural history cohort scored significantly lower at 12%, compared to 74.7% in the OTL-200 arm. While 13 (62%) children in the OTL-200 arm were classified as pre-symptomatic and 8 (38%) children were classified as early symptomatic, all 31 children in the natural history cohort were classified as symptomatic. As a result, compared with the natural history cohort, the OTL-200 arm includes children with milder cognitive and motor impairments at the time of enrolment.

The pharmaceutical company justifies the comparability of the examined patient populations to OTL-200 and the natural history cohort within the framework of the written statement procedure by stating that there were no statistically significant differences between the groups with regard to potential prognostic factors in terms of genotype, disease type and age at the estimated symptom onset.

The statements submitted in the written statement and oral hearing procedures, as well as the subsequently submitted information, could not eliminate the uncertainties as to the extent to which the course of the disease is sufficiently comparable by the presence of symptoms and the manifestations of the disease of the patient groups covered by the therapeutic indication so that analysis without differentiation of the patients seems appropriate. Therefore, in the context of the benefit assessment, the relevant population was differentiated, following the subdivision in the therapeutic indication with regard to existing symptoms and the manifestation of the disease, into children with the form occurring in late infancy (late infantile) or early childhood (early juvenile) without clinical manifestation of the disease, and children with the form occurring in early childhood (early juvenile) with early clinical manifestation of the disease, but who still have the ability to walk independently, before the onset of cognitive decline.

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

A sibling analysis is available for this patient population as a sub-population of the integrated dataset. The sibling analysis conducted included 12 children, who were treated with OTL-200 and had a sibling in the natural history cohort, and 11 siblings in the natural history cohort. The statements submitted in the written statement and oral hearing procedure showed that the clinical courses of siblings are comparable in terms of both time course and extent of symptomatology so that it can be assumed that the onset of symptomatology in the still pre-symptomatic children would be expected in the natural course of the disease during the study observation period. In addition, the descriptive presentation on the characteristic "age at estimated symptom onset" can be considered predictive of disease progression. Even if the

comparison between the siblings in the OTL-200 arm and the corresponding siblings from the natural history cohort can be considered for the benefit assessment, the limitations and uncertainties associated with an indirect comparison without a bridge comparator remain.

Consequently, the risk of bias at the study and endpoint level is considered to be high. Nevertheless, the presented comparison is used for the benefit assessment due to the large effects in the morbidity endpoint category, which cannot be explained solely by random effects based on these uncertainties. Due to the very similar course of the disease in siblings, it is assumed that the comparison arms are sufficiently structurally similar that quantification of the additional benefit is possible even without randomisation. The severity and progressive course of the disease are also taken into account, which is very likely to lead to severe physical limitations, even death in the natural course of the disease. Since the sibling analysis in the OTL-200 arm included almost exclusively pre-symptomatic children, statements can be made here for this patient population regarding quantification of the additional benefit.

Mortality

In the sibling analysis, 0 events occurred in children treated with OTL-200, and 4 events occurred in the natural history cohort. There is a statistically significant difference between the treatment groups in favour of OTL-200. Overall, however, the observation period of the children treated with OTL-200 is too short to derive reliable statements on the quantification of the additional benefit.

Morbidity

GMFC (Gross Motor Function Classification)-MLD Level

The GMFC-MLD is a classification system for describing gross motor function in children with MLD who are at least 18 months old. The classification system comprises seven different levels. Gross motor function is assessed as directly relevant to the patient. The pharmaceutical company submits a time-to-event analysis on the "age to GMFC-MLD level ≥ 5". The loss of the ability to move around independently and to sit independently (GMFC-MLD level ≥ 5) can be understood as a transition to a severe stage of the disease.

In the sibling analysis, 1 event (8%) occurred in OTL-200-treated children, whereas 11 events (100%) were reported in the natural history cohort. The natural history study showed a loss of the ability to move and sit independently at a median age of 3.6 years. However, it should be noted that in the OTL-200 arm, 58% of patients were already censored by 2 years of age, and thus GMFC-MLD levels were no longer determined for more than half of the children treated with OTL-200 at an age when children in the natural history cohort showed a loss of motor function. Due to the lack of information on censoring reasons, the endpoint is only used supplementary.

Survival without severe motor impairment (sMFS)

The sMFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories.

In the time-to-event analysis submitted by the pharmaceutical company for "age to GMFC-MLD level ≥ 5", it was found that, as described above, 7 (58%) of the 12 siblings treated with OTL-200 were censored up to an age of about 2 years. The natural history cohort showed a loss of ability to move and sit independently at a median age of 3.6 years. Data on the duration of observation in the respective comparison arms were not identified.

Compared with the evaluation for "age to the time of death", censoring at the GMFC-MLD level occurred at a much earlier time point. In contrast, no censoring was present in the natural history cohort when evaluating for "age to GMFC-MLD level ≥ 5". Thus, in the analyses of the combined endpoint sMFS, only deaths were included as events for more than half of the children from the OTL-200 arm from 2 years of age. On the other hand, only a deterioration in gross motor function was recorded as an event for children in the natural history study.

The comparison presented for the "survival without severe motor impairment (sMFS)" endpoint is not valid. No statements on the quantification of the additional benefit can be derived.

GMFM (Gross Motor Function Measure)

The GMFM comprises a total of 88 test tasks that are based on a healthy 5-year-old child with normal motor development and can usually be performed without difficulty. The GMFM score is dependent on age. Most healthy children reach their maximum GMFM score (100%), usually at the age of 5.

The aspects of motor development covered by the GMFM are patient-relevant.

Relevant uncertainties exist for the endpoint, particularly in view of the partially retrospective data collection.

There is a dramatic effect for the GMFM endpoint compared to the natural history cohort. There was no manifestation of disease 3 years after treatment with OTL-200. The siblings of the natural history control showed severe motor impairments at this time.

The present indirect comparison is considered to be sufficiently valid due to the very similar course of the disease in siblings. Overall, against the background of the severe course of the untreated siblings and the present effect size, a very clear advantage can be derived in the morbidity endpoint category despite the uncertainties of the historical comparison and the partially retrospective data collection described above.

Quality of life

No endpoints from the quality of life category were assessed.

Side effects

In the absence of safety data on the sibling analysis, results on safety endpoints were presented descriptively for individual study phases in the integrated dataset (IDS), comprising the four marketing authorisation studies. These results are used as they are only available for the total population.

From the start of busulfan conditioning until the respective data cut-off, most AEs with CTCAE grade ≥ 3 were reported in SOC Blood and lymphatic system disorders and PT Febrile neutropenia, but also in SOC Gastrointestinal disorders and PT Stomatitis. All AEs coded with PT Febrile neutropenia, and PT Stomatitis in this study phase were severe AEs. This is analogous at the PT level for aphasia, ataxia, dysarthria, cognitive impairment, motor dysfunction, and spasticity (SOC Nervous system disorders) and for gait disorders (SOC General disorders and administration site conditions).

Due to the duration of observation in the studies and the small number of children treated with OTL-200, a conclusive assessment regarding the safety of OTL-200 is not possible.

No data on adverse events are available for children from the legacy control. Therefore, based on the available data, no conclusions can be made regarding the quantification of the additional benefit in the side effects endpoint category for OTL-200.

Overall assessment

For the assessment of the extent of additional benefit of OTL-200, results of an integrated dataset from the four marketing authorisation studies compared to a historical control are available. This does not allow quantification of the additional benefit, in particular, due to existing uncertainties as to the extent to which the course of the disease is sufficiently comparable due to the presence of symptoms and the manifestations of the disease in the patient groups covered by the therapeutic indication so that analysis without differentiation of the patients appears appropriate.

The quantification of the additional benefit was mainly based on the sibling analysis. Despite the uncertainties and limitations also present in the sibling analysis, the presented comparison is used for the quantification of the additional benefit due to the very similar disease course in siblings and the associated sufficient structural equality of the comparison arms, the large effects in the morbidity endpoint category, which cannot be explained solely by random effects based on these uncertainties.

This also takes into account the severity and progressive course of the disease, which, in the natural course of the disease, is very likely to lead to severe physical limitations, even death.

For overall survival, the sibling analysis showed a statistically significant difference in favour of OTL-200 over the natural history of the disease. Overall, however, the observation period of the children treated with OTL-200 is too short to derive reliable conclusions for this endpoint.

For the morbidity endpoint category, results are available for the GMFC (Gross Motor Function Classification)-MLD Level and GMFM (Gross Motor Function Measure) endpoints. Here, despite existing uncertainties of the historical comparison as well as the partially retrospective endpoint survey, mainly based on the results of the GMFM, a dramatic effect can be derived compared to the natural history control. There was no manifestation of disease 3 years after treatment with OTL-200. The siblings of the natural history control showed severe motor impairments at this time. Overall, a very clear advantage for OTL-200 can be derived for the morbidity endpoint category.

No data are available for the quality of life endpoint category.

For the side effects endpoint category, an assessment of the extent of additional benefit of OTL-200 is not possible. Thus, the overall significance of the present results can only be evaluated to a limited extent due to the lack of control data and the small patient population.

In the overall evaluation of the present partly dramatic effects in patient-relevant endpoints, as well as against the background of the high probability of severe physical and cognitive impairments up to death in untreated children, a very clear advantage of OTL-200 in the morbidity endpoint category can be derived. Overall, the G-BA found a major additional benefit for OTL-200 in the treatment of children with forms of MLD occurring in late infancy (LI) or early childhood (EJ) without clinical manifestations of the disease.

Significance of the evidence

The assessment of the extent of additional benefit of OTL-200 is based on single-arm studies compared with a historical control group. Single-arm studies and legacy comparisons are generally subject to a high risk of bias. Also, for the comparison used for the benefit assessment, the extent of the risk of bias is to be regarded as high for all available endpoints. In addition, only very limited case numbers are available for the benefit assessment of OTL-200.

In the overall view, therefore, a hint for an additional benefit is assumed.

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

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

Justification

For the evaluation of OTL-200 for the treatment of metachromatic leukodystrophy (MLD), characterised by mutations in both alleles of the gene encoding arylsulfatase A (ARSA), which leads to a reduction in ARSA enzymatic activity, results are available from an integrated dataset, comprising the four marketing authorisation studies compared to a historical control for the natural history of the disease (TIGET NHx study). This dataset includes data on both children with the EJ form of metachromatic leukodystrophy with early clinical manifestations of the disease but who still have the ability to walk independently before the onset of cognitive decline and pre-symptomatic children. With regard to this integrated dataset, there are uncertainties as to the extent to which the course of disease due to the presence of symptoms and the manifestations of the disease of the patient groups covered by the therapeutic indication is sufficiently comparable and transferable to the patient group to be considered separately here, for which no separate evaluations are available. Therefore, the data basis is not sufficient to quantify the additional benefit.

In the overall assessment, the G-BA classifies the extent of the additional benefit of OTL-200 on the basis of the criteria in Section 5, paragraph 8, sentence 1, 2 in conjunction with Section 5, paragraph 7, sentence 1, number 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable, because the scientific data basis does not allow a quantification. The significance of the evidence is categorised as a 'hint'.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of XYZ finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a paragraph 1 SGB V.

The European Medicines Agency (EMA) has requested the submission of the final study report of the ongoing marketing authorisation study 201222 with the active ingredient atidarsagen autotemcel for 31 March 2024.

It is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of atidarsagen autotemcel since additional clinical

data regarding the two patient populations concerning overall survival and sustainability of the effects in the endpoint category morbidity are expected, which might be relevant for the assessment of the medicinal product. The limitation allows the inclusion of the expected results from the marketing authorisation study 201222 in the benefit assessment of the medicinal product according to Section 35a SGB V. For this purpose, a limitation of the resolution until 1 July 2024 is considered appropriate.

Conditions for the limitation:

For the new benefit assessment after the expiry of the deadline, a separate presentation of the results of the marketing authorisation study 201222 for patients with and without clinical manifestations of the disease is to be performed in the dossier for all patient-relevant endpoints that are used to prove an additional benefit. In particular, a sibling analysis should be submitted for patients without clinical manifestations of the disease.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long. In accordance with Section 3 paragraph 7 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product atidarsagen autotemcel recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of atidarsagen autotemcel (Section 4, paragraph 3, number 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment for the medicinal product atidarsagen autotemcel can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the active ingredient atidarsagen autotemcel (hereinafter OTL-200). Libmeldy was approved as an orphan drug and is indicated for 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 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. In the therapeutic indication to be considered, two patient groups are distinguished:

a) Children with late infantile (LI) or early juvenile (EJ) forms of 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

On a) For this patient group, the indirect comparison for the overall population presented with the dossier cannot be used to quantify the additional benefit due to methodological limitations. Therefore, the performed sibling analysis is mainly taken into account, considering the severity and the progression of the disease-. Although it is also associated to limitations

and uncertainties, the presented comparison is used for the quantification of the additional benefit due to the very similar disease course in siblings and the associated sufficient structural equality of the comparison arms, the large effects in the morbidity endpoint category, which cannot be explained solely by random effects based on these uncertainties. Since the sibling analysis in the OTL-200 arm included almost exclusively pre-symptomatic children, statements can be made here for this patient population a) regarding quantification of the additional benefit.

For overall survival, the sibling analysis showed a statistically significant difference in favour of OTL-200 over the natural history of the disease. Overall, however, the observation period of the children treated with OTL-200 is too short to derive reliable conclusions on the additional benefit.

For the morbidity endpoint category, a dramatic effect of OTL-200 compared to natural history control can be derived, mainly based on the results for GMFM (Gross Motor Function Measure).

No data are available for the quality of life endpoint category.

For the side effects endpoint category, a conclusive assessment of the safety of OTL-200 is not possible due to the observation durations to date, the small number of children treated with OTL-200, and the lack of control data.

Overall, the G-BA finds a hint of a major additional benefit for OTL-200 for patient group a).

The resolution of the GBA is limited to 1 July 2024.

On b) For this patient group, results from an integrated dataset comprising the four marketing authorisation studies are available in comparison to a historical control for the natural course of the disease (TIGET NHx study). However, no quantification of the additional benefit can be made as no separate evaluations are available for this patient population. In the overall assessment of the data relevant for the benefit assessment, the G-BA classifies the additional benefit of OTL-200 for patient group b) as non-quantifiable because the scientific data basis does not allow a quantification. The significance of the evidence is categorised as a 'hint'.

The resolution of the GBA is limited to 1 July 2024.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI). The information refers to the total population of patients with and without clinical manifestations of MLD. The calculation of the SHI target population refers exclusively to children with MLD who are born each year, thus falling newly into the SHI target population. Under this assumption, the stated range of the SHI target population is plausible overall in the order of magnitude, despite the uncertainties that also result from the determined percentage of MLD patients with the disease forms LI-MLD and EJ-MLD in the relevant disease stages according to the therapeutic indication.

2.3 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 Libmeldy 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.

2.4 Therapy costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2021).

Atidarsagen autotemcel is administered as a single intravenous infusion according to the information provided in the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Atidarsagen autotemcel	Single dose	1	1	1

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Atidarsagen autotemcel	3 – 30 × 10^6 CD34+-cells/kg	3 – 30 × 10^6 CD34+-cells/kg	1 single infusion bag	1	1 single infusion bag

Costs:

Costs of the medicinal products:

Atidarsagen autotemcel is listed in the LAUER-TAXE®, but is only dispensed as a clinic pack. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance, and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19 % value-added tax, in deviation from the LAUER-TAXE® data usually taken into account.

Designation of the therapy	Packaging size	Costs (purchase price clinic pack)
Atidarsagen autotemcel	1 single infusion bag	€ 2,875,000[2]

LAUER-TAXE® last revised: 15 October 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services when using the medicinal product to be assessed in accordance with the product information or directions for use, the costs incurred for this are to be taken into account as costs for additionally required SHI services.

[2] The medicinal product is exempt from value added tax at the applicable LAUER-TAXE® used.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Atidarsagen autotemcel is a cell product derived from autologous CD34+ stem cells. Therefore, mobilisation of HSC (hepatic stellate cells) and leukapheresis are usually necessary to obtain the cell material. Since HSC mobilisation and leukapheresis are 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.

Complete myeloablative conditioning must be performed prior to infusion of atidarsagen autotemcel. Since this is done exclusively in the context of inpatient care, the additional costs incurred by the SHI in the inpatient area are presented in the resolution. The product information of atidarsagen autotemcel does not contain any specifications on the type and duration of the medicinal products to be used for conditioning. In addition, the costs of the active ingredients used for this purpose (e.g. for the active ingredient busulfan used in the clinical studies) may be incurred in the form of hospital-specific additional charges. Therefore, the additional SHI benefits required are not quantifiable.

Designation of the therapy	Costs
Myeloablative conditioning	incalculable

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 29 April 2021, the pharmaceutical company submitted a dossier for the benefit assessment of atidarsagen autotemcel to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 2 August 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 23 August 2021.

The oral hearing was held on 6 September 2021.

An amendment to the benefit assessment with a supplementary assessment was submitted on 27 September 2021 and another one on 14 October 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the subcommittee sessions on 12 and 26 October 2021, and the draft resolution was approved.

At its session on 4 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	27 July 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	31 August 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 September 2021	Conduct of the oral hearing
Working group Section 35a	14 September 2021 21 September 2021 5 October 2021 19 October 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal product	26 October 2021	Concluding discussion of the draft resolution
Plenum	4 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 November 2021

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

Prof. Hecken