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 Cerliponase Alfa (reassessment after the deadline (type 2 neuronal ceroid lipofuscinosis))

of 15 December 2022

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 rare diseases (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 German Social Code, Book Five (SGB V). 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 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 € 30 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, paragraphs 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 approval 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 turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for cerliponase alfa in accordance with Chapter 5 Section 8, paragraph 1, number 5 of the Rules of Procedure of the G-BA (VerfO) is 1 July 2022. 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 June 2022.

Cerliponase alfa for the treatment of type 2 neuronal ceroid lipofuscinosis 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.

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 approval 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 4 October 2022 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 evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G22-25) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering 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 cerliponase alfa.

[1] General Methods, version 6.1 from 24.01.2022. 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 Cerliponase Alfa (Brineura) according to the product information

Brineura is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency**.**

Therapeutic indication of the resolution (resolution of 15. December 2022):

- see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of cerliponase alfa is assessed as follows:

For patients with neuronal ceroid lipofuscinosis (NCL) type 2, also known as tripeptidyl peptidase 1 (TPP1) deficiency, there is a hint for a major additional benefit.

Justification:

In the previous benefit assessment procedure for the active ingredient cerliponase alfa, the G-BA limited the resolution of 21 December 2017 with the condition that, after the expiry of the limitation, the G-BA be provided with registry data for the patients treated with cerliponase alfa in Germany, the final data from the 190-202 study, and data from the EMA conditions (190-504 study and 190-203 study) in order to enable a more reliable assessment of the extent of the additional benefit with regard to patient-relevant endpoints (mortality, morbidity, quality of life and side effects) and on the basis of long-term therapy with cerliponase alfa.

For the new benefit assessment of the active ingredient cerliponase alfa, the pharmaceutical company submitted data from the following single-arm studies in accordance with the limitation requirements: the 190-201 pivotal study, the 190-202 extension study, the 190-203 study (post-authorisation efficacy study), the 190-504 study (post-authorisation safety study), the 190-901 study (external control study on the natural course of the disease), and the DEM CHILD RX study (registry study).

190-201/202 approval study: The 190-201 study is an open-label, single-arm phase I/II study divided into two phases: In the first phase, there was a dose escalation (initially 30, 100 or 300 mg cerliponase alfa ICV every 2 weeks for at least 4 weeks each); in the second phase, cerliponase alfa was administered at a stable dose of 300 mg ICV every 2 weeks for at least 48 weeks. 24 patients with a confirmed CLN2 diagnosis, who were between 3 and 15 years of age at the start of the study and had a score of 3 to 6 on the modified Motor-Language (ML) scale and a score of at least 1 in each of the two domains, were enrolled in the study. After completion of the 190-201 study, the study participants could switch to the open-label, single-arm 190-202 extension study. All patients in the ITT population of the 190-201 study (N = 23) crossed over to the 190-202 study (one subject in the 190-201 study withdrew consent after

one infusion). In the extension study, patients were treated with cerliponase alfa for up to 240 weeks. The studies have been completed.

In addition to safety, the primary endpoint in the 190-201/202 studies was the efficacy of cerliponase alfa as measured by the Hamburg Motor-Language (HML) scale and modified Motor-Language (ML) scale, respectively, compared to an untreated external control group. Results were presented on the final data cut-off of the extension study (referred to as the 190-201/202 study) from 10 December 2020. The median treatment duration from study baseline was 286 weeks (min; max: 0.1; 309.1).

The 190-201 study was conducted between September 2013 and November 2015 in 5 study sites in Germany, the UK, the USA and Italy. The 190-202 study was conducted between February 2015 and December 2020 in 4 study sites in Germany, the UK, the USA and Italy.

The 190-203 (PAES) study: This is an open-label, single-arm prospective phase II intervention study. Fourteen patients < 18 years of age with a confirmed CLN2 diagnosis and a score of 3 to 6 on the modified ML scale were enrolled in the study. The treatment duration is 144 weeks.

The primary endpoint will include the delay in disease progression, assessed using the CLN2-ML scale, compared to an untreated external control group. Results were presented for the interim data cut-off of 26 April 2020 and for the serious adverse event results for the interim data cut-off of 26 April 2021, respectively. The median treatment duration (data cut-off April 2020) was 141.9 weeks (min; max: 64.4; 142.6).

The ongoing study has been conducted since January 2016 in 4 study sites in Germany, UK, USA and Italy.

The 190-504 (PASS) study: The 190-504 study is an open-label, non-interventional observational study. The study is designed to follow up subjects who have previously started treatment with cerliponase alfa (e.g. in clinical studies) or who wish to start treatment with cerliponase alfa within 60 days of enrolment in the study. 40 patients with a confirmed CLN2 diagnosis were enrolled in the study. 2 subjects were enrolled in the studies but not treated, therefore the safety population includes only 38 subjects instead of 40. The examinations and treatments of the participants should be carried out according to local standards and the data collected at least every 6 months for up to 10 years.

The primary endpoint will be the long-term safety of cerliponase alfa. For the benefit assessment, results were submitted for the interim data cut-off from 26 April 2022. The median observation time from enrolment in the study to interim data cut-off is 0.9 years (min; max: 0.0; 2.5), median treatment duration with cerliponase alfa 4.1 years (min; max: 1.1; 8.6). 36 subjects started cerliponase alfa treatment prior to enrolment in the study.

The study is ongoing and has been running since October 2019 in 11 study sites in Germany, Italy, France, Sweden, Denmark, the Netherlands and the UK.

190-901 study: For the 190-901 study, data excerpts with different data cut-offs (see section "Indirect comparisons") from the DEM-CHILD registry were used and analysed with the main aim of being able to describe the natural course of the disease in a larger patient collective without treatment with cerliponase alfa and to use it as an external control.

The original DEM CHILD database is an ongoing, multicentre, multinational, clinical database in the Hamburg study site. The database collects clinical, laboratory and imaging data as well as information on the development of subjects with NCL (including CLN2). The DEM-CHILD registry contains data on the natural course of the disease from 2 hospitals in Hamburg and Verona.

DEM CHILD RX study: Since its approval in 2017, data from subjects treated with cerliponase alfa have been collected within the DEM-CHILD registry. In addition, subjects treated with cerliponase alfa from the Compassionate Use Programme of 2016 are included.

The registry included 52 subjects treated with cerliponase alfa in Germany. 23 of these subjects were treated with cerliponase alfa in clinical studies, and 29 subjects started treatment with cerliponase alfa outside of clinical studies (as part of the marketing authorisation or under the Compassionate Use Programme). Of these 29, 24 patients with a confirmed CLN2 diagnosis, who had a follow-up of at least 6 months (i.e. at least 2 examinations using the HML scale) until December 2020 and at least two assessments on the ML scale with scores between 1 and 6 at intervals of at least 6 months, were included in the DEM CHILD RX study. Follow-up data of less than 6 months were available for 5 subjects. These were classified as non-evaluable by the pharmaceutical company.

The main objective of the registry study was to analyse the treatment effect of cerliponase alfa in the German healthcare context. Endpoints included overall survival and disease progression measured by the HML scale. For the benefit assessment, the results were presented with data cut-off from December 2020. The median observation period is 78 weeks (min; max: 22.4; 218.6).

Using the registry data on disease progression, the efficacy of cerliponase alfa (DEM-CHILD-RX population) was to be investigated within an indirect comparison to the external control (untreated subjects in DEM-CHILD).

The patients were enrolled in Hamburg between 2016 and December 2020.

Indirect comparisons

With the current dossier, the pharmaceutical company submits indirect comparisons without a bridge comparator for the intervention studies 190-201/202 (data cut-off 30.11.2015 and final data cut-off 10.12.2020), and 190-203 (interim data cut-off 26.04.2020), as well as for the DEM CHILD registry study (data cut-off December 2020). The 190-901 study (natural history of disease) is used as an external control for the intervention studies.

Due to the longer observation period, the final data cut-off of the 190-201/202 study (median observation period 286 weeks) is used in the present procedure. All subjects in the ITT population of the 190-201 study switched to the 190-202 study.

From the 190-901 study, using different data cut-offs ("update") and additionally using different filter criteria, a population "Natural History (NH) - Update 2" (data cut-off August 2016) was used as external comparison for the 190-203 study and a population "NH - Update 3" (data cut-off February 2021) was used as external comparison for the 190-201/202 and DEM CHILD RX studies.

The filter criteria for the NH Update 2 population as an external comparison for the 190-203 study were as follows: "at least one HML score ≥ 3" and "at least two HML scores between 1 and 6 and at least 6 months apart".
For the NH update 3 population as external comparison for the 190-201/202 study, the filter criteria "at least one HML score ≥ 3 at age ≥ 36 months" and "at least two HML scores between 1 and 5 and at least 6 months apart" were applied. Also excluded was one twin and 7 subjects who participated in the 190-201/202 study. The filter criteria were applied in orientation to the inclusion and exclusion criteria of the intervention studies.
For the external comparison for the DEM CHILD RX study, the filter criterion "at least two HML scores between 1 and 6 and at least 6 months apart" was applied, and 2 subjects who switched to the DEM CHILD RX study were also excluded. Following application of the filter criteria, 77% (n=53) and 61% (n=42) and 75% (n=52) of the 190-901 study (N = 69) entered the evaluable patient populations NH update 2 and NH update 3, respectively (external comparison for the 190-201/202 study and for the DEM CHILD RX study).

For the indirect comparisons without bridge comparator, matching was performed with 2 (same ML/HML score at baseline, age difference ≤12 months each at baseline) and with 3 criteria (same ML/HML score at baseline, age difference ≤3 months each at baseline, same number of common alleles (c.622C→T, c.509.1G→C)).
For the indirect comparison of the final data cut-off of the 190-201/202 study, a 1:1 matching with 3 criteria was defined a priori. Since the influence of genotype on disease progression is unclear and the analysis population is reduced by considering genotype as a matching factor, the post-hoc analysis with a matching with 2 criteria is considered more relevant and is presented in the resolution. For the indirect comparison to the 190-203 study, no matching with 2 criteria was presented, but a priori a 1:3 matching with 3 criteria was defined and performed.
In addition, an evaluation was carried out by the pharmaceutical company using the complete data set without matching (naïve indirect comparison). Since the intervention and control populations were not matched for this evaluation, it is regarded as subordinate to the evaluation based on the matched populations and is not presented in the resolution.

For the indirect comparison without a bridge comparator between the DEM-CHILD RX study and the 190-901 NH3 population, a 1:1 matching with 2 criteria was performed.

Uncertainties of the indirect comparisons

The DEM-CHILD registry is the largest database of international CLN2 disease patient data to date. Both cerliponase alfa-treated and untreated subjects were included in the two study sites of Hamburg and Verona. Since the market launch of cerliponase alfa in 2017, almost all living CLN2 patients in the DEM-CHILD registry have received cerliponase alfa. However, it cannot be conclusively assessed to what extent the available data from only two sites of the DEM CHILD registry and the selection of evaluable populations from the 190-901 study, as well as the selection of the evaluable population of subjects treated with cerliponase in the DEM CHILD registry outside of clinical studies, may have led to selection effects. According to the written statement, the pharmaceutical company only had data for the evaluable population described (DEM CHILD RX dataset).

In their written and oral statements, the clinical experts pointed out that all CLN2 patients, who were treated with cerliponase alfa in Germany after marketing authorisation and were not enrolled in one of the two intervention studies 190-201/202 or 190-203, were offered the opportunity to participate in the independent DEM-CHILD-RX observational study. Furthermore, there was no selection according to disease severity grade when the observational study was included, so that the DEM-CHILD RX cohort also included patients in significantly more advanced disease stages than the intervention studies.
Furthermore, the HML score in the historical comparator study (190-901 study) was partly retrospectively and historically different from the 190-201/202 and 190-203 intervention studies and the DEM CHILD RX registry study. Here, too, it cannot be assessed to what extent this has resulted in distortions with regard to the results of the historical comparison. However, there are no indications that the risk of bias resulting from retrospective data collection has only had an effect in one direction (over- or underestimation).
For the certainty of results of a historical comparison, the completeness of the information and a sufficient agreement of the characteristics of the study populations considered are also essential. During the written statement procedure, the pharmaceutical company submitted information and data on the patient flow of the DEM-CHILD registry and the external controls formed from it, on the baseline and patient characteristics of the historical control populations and the treated study populations (190-201/202 and 190-204 studies, DEM-CHILD RX study), as well as on the observation periods of the 190-201/202 and 190-203 studies.
For the intervention studies or the registry study and the associated external controls, corresponding information is available on patient characteristics and observation periods before and after matching (with the exception of the observation period before matching of the 190-901 NH3 study for the indirect comparison with the DEM CHILD RX registry study). In some cases, imbalances in genotype, sex and the appearance of first symptoms ("speech difficulties", "motor difficulties", "seizures") could be observed. The patients in the external controls 190-901 NH2 were approximately one to two years older than the ITT or matched population of the 190-203 study before and after matching at disease onset and diagnosis. There are also partial imbalances in individual HML scores.
Information on previous therapies, concomitant therapies or previous diseases is mostly not available, so that a comparison of the study populations under consideration is not possible with regard to concomitant medication in particular. The extent to which the lack of these data would have a relevant influence on the outcome of the benefit assessment remains open.
A valid comparison requires sufficient structural equality of the patient population as well as knowledge and consideration of all relevant confounders and effect modifiers as adjustment variables. It is not clear from the pharmaceutical company's documents how the confounders defined in the study documents were identified and selected. However, according to the opinion of the clinical experts, apart from age at onset, certain genotypes and treatment with cerliponase alfa, there are no known factors that influence the course of neurodegeneration in CLN2 patients. According to the clinical experts, matching patients on baseline ML score and age therefore ensures structural equality between the comparator groups.
There are no publications on the possible influence of certain genotypes; this will be investigated in the 190-504 study.

Mortality

No deaths were reported in the 190-201/202 and 190-203 studies. Up to the time of the data cut-off, no patients in the DEM CHILD RX study and 190-504 study had died.

For the indirect comparison of the 190-201/202 study and external control 190-901 NH3, the results for 1:1 matching (2 criteria) are presented in the resolution. As no deaths occurred in the intervention study, an adequate calculation of the hazard ratio is not possible. However, there is a statistically significant difference in favour of the intervention of cerliponase alfa treatment.

In addition, the analysis for a 1:1 matching with 3 criteria, which is evaluated here as supportive, shows a comparable result. The supportive analysis for the naïve indirect comparison also shows a comparable result. Since no adjustment of the intervention and control populations for the confounders age and baseline ML/HML score considered relevant was made for the evaluation of the naïve indirect comparison, this is not considered here.

For the indirect comparison between the DEM CHILD RX registry study and 190-901 NH3, only an evaluation without matching (naïve comparison) was presented for the endpoint "overall survival". For the external patient population 190-901 NH3 (N=52), no information could be identified on the median observation periods recorded for the endpoint "from birth". Even before the first death in the external control, about 8 to 10 subjects (33-42%) were censored from the DEM CHILD RX registry study (N=24).
In addition, information on the HML/ML score at baseline of the evaluable population, for example, was not provided, so that it cannot be conclusively assessed to what extent the disease stage, measured by the HML/ML score, differs between the DEM CHILD RX registry study and the external control. Due to these limitations, a risk of bias of the results in favour of the intervention cannot be excluded. Additional sensitivity analyses to check the robustness of the results were not presented.

48% of the patients in the external control died, while no deaths were observed in the DEM-CHILD-RX registry study. The naïve indirect comparison without matching between the DEM CHILD RX registry study and 190-901 NH3 for the endpoint "overall survival" is only presented additionally in the resolution due to the uncertainties mentioned and is not taken into account for the determination of the extent of additional benefit.

For the indirect comparison between the 190-203 study and the external control 190-901 NH2, no evaluation was performed for the endpoint "overall survival".

Despite the uncertainties associated with the historical comparison presented, a comparison on the objective endpoint of overall survival between the intervention study and the historical control seems plausible due to the deterministic and lethal course of the disease. Due to the magnitude of the difference found and the consistency in the supportive analysis, it is also assumed that it can be ruled out that the difference is based solely on a systematic risk of bias due to the historical comparison.

Morbidity

CLN-2 rating scale: ML/HML scale

To assess disease progression, an HML scale (Hamburg Motor-Language Scale) developed for neuronal ceroid lipofuscinosis type 2 (CLN2) disease was adapted for the single-arm 190-201/190-202 studies with the developers of the HML scale to obtain objective anchor points on the one hand and to clarify the demarcation between categories on the other. Both the HML scale and the ML scale (0-6 points) include only two domains (motor skills and language ability) out of the original total of four domains of the global scale (MLVS), which also included the domains of vision and epileptic seizures. Motor skills and language ability are assessed on a 4-point scale (0-3 points), with individual gradations within both domains describing normal abilities (3 points) to complete loss of function (0 points). The scales record delimitable milestones of motor and language skills. For example, the loss of a score from 2 to 1 in the motor domain is characterised by a change from a still possible independent walking of ≥ 10 steps to no longer possible independent walking. The domains of vision and epileptic seizures were not recorded in the HML scale or the ML scale. Although these domains are considered important endpoints in CLN2 disease, the use of the motor and language domains can be considered sufficient for assessing disease progression in the present case. Taking into account the natural course of the disease in patients with confirmed CLN2 disease, a preservation or improvement of these motor and linguistic abilities addressed in the HML scale or in the ML scale appears to be comprehensible and relevant to the patient. However, a methodologically adequate validation of the scales is only available to a limited extent.

Change in CLN-2 rating scale from baseline

At week 281, the 190-201/202 study shows a mean score reduction of 1.2 points on the ML scale.

The 190-203 study shows a mean score reduction of 0.4 points on the ML scale by week 145.

For the 190-201/202 and 190-203 studies, the results of the change from baseline for the MLV (ML scale plus "vision") and MLVS scales (ML scale plus "vision" and "seizures") were also presented descriptively in the dossier. However, for the two domains "seizures" and "vision" or for the MLV and MLVS global scales, information on the development and validation process is missing, so that no assessment is possible with regard to validity. Therefore, only the results of the HML scale or the ML scale are presented in the benefit assessment.

For the 190-504 study, baseline data on the CLN2 rating scale were available for only 24 subjects (60.0%) of the analysis population (N = 40). The results are therefore not taken into account in the benefit assessment.

For the DEM CHILD RX registry study, results are reported only for the indirect comparison without bridge comparator after matching, but not for the analysis population before matching (N = 24). Results for the change in the CLN-2 rating scale from baseline are accordingly not available.

Time to disease progression

In the resolution, the "time to disease progression" for the 190-201/202 study, defined as an irreversible loss of ≥ 2 points on the CLN-2 rating scale (any decline of 2 points or more that did not improve at the last recorded observation) or an irreversible score of 0 (deterioration to 0 points that did not increase to a score > 0 at the last recorded observation).

During the median treatment duration of 286 weeks, 52% of patients in the 190-201/202 study experienced an irreversible loss of ≥ 2 points or an irreversible score of 0 at a median duration of 272 weeks. In 48% of patients, no irreversible loss of ≥ 2 points or an irreversible score of 0 occurred during the treatment duration, these were censored at the last CLN2 score collection.

For the indirect comparisons of the 190-201/202 study and the 190-901 NH3 external control and the 190-203 study with the 190-901 NH2 external control, the results for time to disease progression according to 1:1 matching (2 criteria) or according to 1:3 matching (3 criteria) are presented in the resolution for the present benefit assessment.

There are statistically significant differences in favour of treatment with cerliponase alfa.

A similar result was observed for the evaluation of the indirect comparison with 1:1 matching with 3 criteria of the 190-201/202 and 190-901 NH3 studies. In the supportive analyses for "time to an irreversible score of 0", the results for the 1:1 matching with 3 criteria were also comparable to the 1:1 matching with 2 criteria of the 190-201/202 and 190-901 NH3 studies. The supportive analysis for the respective naïve indirect comparisons also shows a comparable result. Since no adjustment of the intervention and control populations for the confounders age and baseline ML/HML score considered relevant was made for the evaluation of the naïve indirect comparisons, these are not considered here.
No sensitivity analyses were performed for the indirect comparison of the 190-203 study with the 190-901 NH2 external control.

Results are available for the indirect comparison of the DEM CHILD RX study and the 190-901 NH3 external control after 1:1 matching with 2 criteria. Sensitivity analyses were not presented.

There was a statistically significant difference in favour of treatment with cerliponase alfa.

Progression rate

The rate of disease progression is measured by the CLN2 disease scale score loss scaled to 48 weeks. The rate of disease progression is presented as a positive number, with higher values corresponding to faster disease progression.

The analysis of the rate of disease progression is fraught with uncertainty due to unclear and insufficiently justified assumptions. It remains unclear, for example, why a linear change is only assumed for ML/HML values between 1 and 5. In addition, information on the collection times of the CLN2 score in the external control is missing.

In the resolution, the progression rate results for the 190-201/202 and 190-203 studies are presented.

For the indirect comparisons of the 190-201/202 study and the 190-901 NH3 external control and the 190-203 study with the 190-901 NH2 external control, the results for time to disease progression according to 1:1 matching (2 criteria) or according to 1:3 matching (3 criteria) are presented in the resolution for the present benefit assessment.

For the indirect comparison of the 190-201/202 study and the 190-901 NH3 external control, there is a statistically significant difference in favour of treatment with cerliponase alfa. A comparable result could be observed for the analysis evaluated as supportive for a 1:1 matching with 3 criteria. The supportive analysis for the naïve indirect comparison also shows a comparable result. Since no adjustment of the intervention and control populations for the confounders age and baseline ML/HML score considered relevant was made for the evaluation of the naïve indirect comparison, the supportive analysis for the naïve indirect comparison is not considered here.

For the indirect comparison of the 190-203 study with the 190-901 NH2 external control after 1:3 matching (3 criteria), a calculation of the p value was not provided for the interim analysis.

Results are available for the indirect comparison of the DEM CHILD RX study and the 190-901 NH3 external control after 1:1 matching with 2 criteria. Sensitivity analyses were not presented.

There was a statistically significant difference in favour of treatment with cerliponase alfa.

EQ-5D-VAS

The Visual Analogue Scale VAS of the EQ-5D-5L (European Quality of Life 5 Dimensions 5 Level Version) is a numerical scale from 0 to 100 on which the patient answers the question about his/her health status at the time of measurement. "0" stands for the worst imaginable health status and "100" for the best imaginable health status.

The patient-reported assessment of health status is classified as patient-relevant.

For the DEM CHILD RX study, a descriptive evaluation of the endpoint was planned.
The endpoint was not assessed or evaluated in the other studies.

In summary, in the morbidity category, there is a clear and consistent advantage of treatment with cerliponase alfa over untreated control in terms of motor skills and speech (measured by M/L scale/ HML scale), which is not called into question by the uncertainties of the historical comparisons mentioned above.

Quality of life

PedsQL

The assessment of general quality of life using the sufficiently validated instrument "PedsQL 4.0 Generic Core Scales" is classified as patient-relevant.

The PedsQL Family Impact Module questionnaire measures the impact of the child's chronic diseases on the family. As the instrument does not directly address the quality of life of the affected children, the instrument is assessed as not directly relevant to patients and is not considered for the present benefit assessment.

The questionnaire was used to survey quality of life in the 190-201/202 study, regardless of the age of the child. At week 193 of the 190-202 study (corresponding to week 242 of the 190-201/202 overall study), there was an average reduction of 15.2 points in the total score compared to baseline of the 190-201 study. For the domains, with the exception of the domain "emotional skills", for which an increase was shown, reductions of varying degrees were evident.

No results on PedsQL were provided for the interim study report of the 190-203 study. The endpoint was not collected in the 190-504 study.

For the DEM CHILD RX study, a descriptive evaluation of the individual dimensions, the psychosocial health sum score and the total score was planned. However, there is no analysable data as the return rate was 75% at baseline and <70% at subsequent visits.

As no comparator data are available, no statements on the extent of additional benefit can be derived from the results for the endpoint PedsQL.

Infant Toddler Quality of Life Questionnaire (IT-QoL-97)

The IT-QoL-97 is a quality of life assessment tool. The pharmaceutical company submitted a validation study in the dossier for a version of the questionnaire other than that used in the DEM CHILD RX registry study. It remains unclear to what extent the results of the validation study are transferable and to what extent the results determined in the validation study in subjects with chronic respiratory disease (predominantly asthma) and healthy subjects are transferable to the present therapeutic indication. The IT-QoL-97 is therefore not considered for the benefit assessment.

The endpoint "IT-QoL-97" was only collected in the DEM CHILD RX registry study.

CLN2 QoL

The CLN2 QoL (Quality of Life) is a questionnaire to assess disease-specific quality of life. The questionnaire comprises 28 items which are assigned to 6 domains. The items are each answered on a Likert scale (from never = 0 to almost always =4) by the parents of the children concerned. After inversion and transformation of the values, scales with a range of 0 to 100 points are obtained; higher values are associated with lower impairment. The questionnaire is only available in English.

The endpoint is classified as a patient-relevant endpoint in the present operationalisation. However, the operationalisation is not completely comprehensible, among other things, because some items are not clearly worded (e.g. item 2 "During seizures, safety becomes a problem" or item 21 "Impulsive or unsafe behaviour"). Methodologically adequate validation is only available to a limited extent. Overall, the wording of the items and the linguistic (translation of the items into the parents' mother tongue) and psychometric validity (including

reliability and convergent validity, ceiling effects) of the instrument are assessed as not sufficiently adequate.

The CLN2-QoL is therefore not considered for the benefit assessment.

The questionnaire was used in the 190-201/202, 190-203 and DEM CHILD RX studies. No endpoint evaluation was provided for the 190-203 study.

In summary, no statements on the extent of additional benefit can be derived for the quality of life category.

Side effects

The 190-201/202 (N = 24) and 190-203 (N = 14) studies performed a descriptive analysis of safety endpoints for the safety population. Recording of all AEs/SAEs occurred after implantation of the intracerebroventricular (ICV) access in the 190-201/202 study, whereas in the 190-203 study recording only started from the first dose of cerliponase alfa according to the study protocol. After implantation of the ICV access and before the first dose of cerliponase alfa, only SAEs related to the study procedures or ICV access were reported.

AEs occurred in all subjects in the safety population in both studies; SAEs were reported in 86% of subjects in the 190-203 study and in approximately 70% in the 190-201/202 study. AEs with CTCAE grade ≥ 3 were reported in summary only for the 190-203 study and occurred in 64% of participants.

In both studies, no participants discontinued study medication due to AEs.

In the 190-504 study, all AEs were recorded from the time of enrolment in the study or from receipt of the first dose. It is unclear to what extent a retrospective survey of safety endpoints was conducted. Subjects with different observation or treatment periods are included in the evaluation. Only very limited information on safety assessment is available for the DEM CHILD RX study.

In addition, for the 190-504 and DEM CHILD RX studies, only treatment-related TEAEs ("Treatment-Emergent Adverse Events") associated with either the study medication or the access device were reported.

In the 190-504 and DEM CHILD RX studies, AEs occurred in 40% and 67% of subjects, respectively. SAEs were reported in 29% of subjects in the 190-504 study. SAEs were not reported for the DEM CHILD RX study. In the 190-504 study, AEs with CTCAE grade ≥ 3 occurred in 21% of subjects. In the DEM CHILD RX study, AEs of grade 3 occurred in one subject (4%) and AEs of grade 4 in 3 subjects (13%).

In both studies, no participants discontinued study medication due to AEs.

Due to the only single-arm, non-comparator data, no statements on the extent of additional benefit can be derived for the category of side effects.

Overall assessment/ conclusion

Despite the aforementioned uncertainties associated with the historical comparisons, the consideration of the historical comparisons overall appears justified based on the very rare

disease, the paediatric patient population and the deterministic disease course. Some of the uncertainties were also addressed by the written and oral statements of the pharmaceutical company and the clinical experts.
In addition, data for longer-term therapy with cerliponase alfa (median treatment duration up to 286 weeks) are available for the current benefit assessment, which corroborate the advantages in morbidity already shown in the initial procedure and extend them by an advantage in mortality.
In the mortality category, there is a clear advantage of treatment with cerliponase alfa over the natural course of the disease. Due to the magnitude and consistency of the difference found, it is assumed that it can be ruled out that the difference is based solely on a systematic risk of bias due to the historical comparison. Similarly, in the morbidity category, there is a clear and consistent advantage for treatment with cerliponase alfa over untreated control in terms of motor skills and speech (measured by M/L scale/ HML scale), which is not called into question by the uncertainties of the historical comparisons mentioned above.
No improvement in quality of life was observed during treatment with cerliponase alfa. However, in the present disease, where treatment success is defined by the absence or slowing of disease progression, improvement in the patients' quality of life cannot necessarily be assumed.
As there are no data on adverse events in the historical control cohort, a comparison with the previous symptomatic therapeutic approach in the presence of neuronal ceroid lipofuscinosis type 2 is still not possible. However, longer-term safety data are available that confirm the side effects profile of cerliponase alfas from the initial assessment. No discontinuations due to AEs or deaths were observed in any of the studies. However, due to a lack of comparator data, no statements on the extent of additional benefit can be derived for the quality of life category and the side effects category. The extent of the advantages of treatment with cerliponase alfa compared to the natural course of the disease in the endpoint of overall survival and in morbidity is classified as major.
In summary, the G-BA therefore classifies the extent of the additional benefit of cerliponase alfa on the basis of the criteria in Section 5, paragraph 7 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as substantial, taking into account the severity of the disease and the therapeutic objective in the treatment of neuronal ceroid lipofuscinosis type 2.

Significance of the evidence

Due to the single-arm study data, the risk of bias at study level and endpoint level is considered high.
Non-adjusted indirect comparisons have a fundamental methodological uncertainty of results even when dramatic effects are observed. In particular, the age difference of one to two years at disease onset and diagnosis between the patients of the external controls 190-901 NH2 and the population of the 190-203 study, as well as missing information on the HML/ML score at baseline of the evaluable population in the indirect comparison between DEM CHILD RX and the external control contribute to the present uncertainty.
For the present benefit assessment, three historical comparisons with data from longer-term therapy with cerliponase alfa (median treatment duration up to 286 weeks) were submitted, which corroborate the advantages in morbidity already shown in the initial procedure and

extend them by an advantage in mortality. Since the same external control population was used for all three historical comparisons, there is further uncertainty regarding the significance of the results.
In both the mortality and morbidity categories, there is a statistically significant advantage of treatment with cerliponase alfa over the natural course of the disease, which is limited in its reliability of data by the uncertainties of the historical comparisons mentioned above. Overall, a hint for an additional benefit is derived.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment the active ingredient cerliponase alfa (Brineura) due to the expiry of the limitation of the resolution of 21 December 2017. Brineura was approved as an orphan drug under "exceptional circumstances" for the treatment of neuronal ceroid lipofuscinosis (NCL) type 2, also known as tripeptidyl peptidase 1 (TPP1) deficiency.
The pharmaceutical company presents data and three indirect comparisons without a bridge comparator for the single-arm 190-201/202 and 190-203 intervention studies, as well as for the single-arm DEM CHILD registry study versus external control populations of the 190-901 study on the natural history of the disease. In addition, data are available for the single-arm 190-504 safety study. Despite the uncertainties associated with the historical comparisons, consideration of the historical comparisons overall appears justified based on the very rare disease, the paediatric patient population and the deterministic course of the disease.
In addition, data for longer-term therapy with cerliponase alfa (median treatment duration up to 286 weeks) are available for the current benefit assessment, which corroborate the advantages in morbidity already shown in the initial procedure and extend them by an advantage in mortality.
In the mortality category, there is a clear advantage of treatment with cerliponase alfa over the natural course of the disease. Due to the magnitude and consistency of the difference found, it is assumed that it can be ruled out that the difference is based solely on a systematic risk of bias due to the historical comparison. Similarly, in the morbidity category, there is a clear and consistent advantage for treatment with cerliponase alfa over untreated control in terms of motor skills and speech (measured by M/L scale/ HML scale), which is not called into question by the uncertainties of the historical comparisons mentioned above.
No improvement in quality of life was observed during treatment with cerliponase alfa. As there are no data on adverse events in the historical control cohort, a comparison with the previous symptomatic therapeutic approach in the presence of neuronal ceroid lipofuscinosis type 2 is still not possible. However, longer-term safety data are available that confirm the side effects profile of cerliponase alfas from the initial assessment. The extent of the advantages of treatment with cerliponase alfa compared to the natural course of the disease in the endpoint of overall survival and in morbidity is classified as major.
Overall, a hint for an additional benefit is derived, as the demonstrated advantages of treatment with cerliponase alfa compared to the natural course of the disease in mortality and morbidity are limited in their reliability of data due to the uncertainties of the historical comparisons. The overall conclusion is that there is a hint for a major additional benefit of cerliponase alfa over the natural course of the disease.

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 G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company.

The procedure of the pharmaceutical company is mathematically largely comprehensible. However, the incidences determined by the pharmaceutical company (newly ill patients with CLN2) are subject to uncertainty, among other things due to the questionable up-to-dateness of the data used. In addition, with the uncertainty range determined by the pharmaceutical company, the transferability of data on untreated patients to patients with CLN2 treated with cerliponase alfa is questionable and the methodological procedure for mapping the uncertainty is not comprehensible. It is also unclear whether all patients diagnosed with CLN2 could be taken into account in the prevalences of treated CLN2 disease calculated by the pharmaceutical company in 2017 and 2022 and to what extent the assumption that none of the treated and newly diagnosed patients will die is correct.

Overall, the number of patients in the SHI target population stated by the pharmaceutical company is therefore fraught with uncertainty.

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 Brineura (active ingredient: cerliponase alfa) at the following publicly accessible link (last access: 5 October 2022):

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

Initiation and monitoring of treatment with cerliponase alfa should only be carried out by doctors experienced in the intracerebroventricular administration of medicinal products.

This medicinal product was approved under “special conditions”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2022).

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of

the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Cerliponase alfa	1 x every 14 days	26.1	1	26.1

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The recommended dose (for patients 2 years and older) according to the product information is 300 mg cerliponase alfa, administered once every other week by intracerebroventricular infusion. A lower dosage is recommended for patients under 2 years of age. However, only the dosage information for patients aged 2 years and older is taken into account for the cost calculation.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Cerliponase alfa	300 mg	300 mg	2 x 150 mg	26.1	52.2 x 150 mg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Cerliponase alfa 150 mg	2 INF	€ 23,628.77	€ 1.77	€ 0.00	€ 23,627.0
Abbreviations: INF = infusion solution					

LAUER-TAXE® last revised: 15 November 2022

Costs for additionally required SHI services:

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

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.

Implantation of an intracerebroventricular access device is done once prior to treatment. The costs for the implantation cannot be clearly quantified. For the intracerebroventricular infusion (with additional laboratory examination of the cerebrospinal fluid) to be carried out every second week, the costs are also not clearly quantifiable; in part, no suitable billing figures are available.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Medicinal product to be assessed				
Cerliponase alfa	Implantation of an intracerebroventricular access device, infusion, laboratory examination of the cerebrospinal fluid	26.1	incalculable	incalculable

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Cerliponase Alfa

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 30 June 2022, the pharmaceutical company submitted a dossier for the benefit assessment of cerliponase alfa to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

The benefit assessment of the G-BA was published on 4 October 2022 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 25 October 2022.

The oral hearing was held on 7 November 2022.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 24 November 2022.

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 session of the subcommittee on 6 December 2022, and the proposed resolution was approved.

At its session on 15 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 September 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	2 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 November 2022	Conduct of the oral hearing
Working group Section 35a	16 November 2022 30 November 2022	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 products	6 December 2022	Concluding discussion of the draft resolution
Plenum	15 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 December 2022

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

Prof. Hecken