Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V – Cerliponase Alfa

of 21 December 2017

Contents

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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 of the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not 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, Nos. 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. Only the extent of the additional benefit must be demonstrated.

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 retail prices including VAT exceeds €50 million in the last 12 calendar months. In accordance with 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 in accordance with 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 compared 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of 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.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by 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 of 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.

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2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient cerliponase alfa in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 July 2017. 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, number 1 VerfO on 30 June 2017.

Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis (NCL) type 2 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 sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit is 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 assess 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 2 October 2017 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 G17-06) prepared by the IQWiG, and the written statements submitted in the written and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) according to 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.

In light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of cerliponase alfa (Brineura®) in accordance with product information

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

2.1.2 Extent of the additional benefit

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

1 General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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For patients with neuronal ceroid lipofuscinosis (NCL) type 2, there is a non-quantifiable additional benefit.

Justification:

To answer the question on the extent of the additional benefit of cerliponase alfa, the results of Study 190-201, which was decisive for the granting of marketing authorisation under "exceptional circumstances", as well as the results of two supportive studies, 190-202 and 190-901, are available.

Study 190-201/190-202

The pivotal Study 190-201 is a first-in-human Phase 1/2 study – a multi-centre, open-label, single-arm intervention study divided into two phases. Phase 1 consisted of dose escalation (≥ 4 weeks per dose level). In other words, patients initially received doses of 30, 100, or 300 mg cerliponase alfa intracerebroventricularly every two weeks for at least four weeks each. In the multi-centre Phase 2, cerliponase alfa was administered stably for at least 48 weeks to 23 patients aged three to 8 years with a confirmed CLN2/TPP1 gene mutation. Study 190-201 included CLN2 patients who were at a mild to moderate stage of disease in order to provide a sensitive measure of symptom deterioration. However, regardless of the stage of disease progression, CLN2 disease is always characterised by a serious course. In addition to the primary endpoint (component score of the adapted Hamburger Scale "ML Scale") to assess the efficacy of cerliponase alfa after 12 months, the study surveyed data on quality of life and safety as well as MRI data and laboratory parameters.

Study 190-202 is an ongoing, multi-centre, open-label, single-arm extension study of Study 190-201, which is expected to end in December 2020 (study duration 239 weeks). All 23 patients who had completed the 48 weeks of Study 190-201 were included. The primary target criterion is the long-term safety of cerliponase alfa in addition to the change in the ML scale (efficacy).

Because studies 190-201 and 190-202 are studies without a control group, a high risk of bias is assumed.

Study 190-901

The results of the uncontrolled pivotal studies 190-201/190-202 were compared with a historical control of untreated patients. The comparison was specified in the Statistical Analysis Plan of the "Integrated Summary of Efficacy" (SAP ISE): The primary endpoint was a responder analysis after 1:1 pairing of participants in Study 190-201 with patients in the historical control group (Study 190-901). Data from the historical control group (Study 190-901) were surveyed as part of the DEM-CHILD patient registry. This is an ongoing, multi-centre and multinational, clinical, pan-European database based in Hamburg. In the historical control group, the originally developed 'HML scale' (combined motor and language domain scale) was used. For the benefit assessment of cerliponase alfa, a data cut-off of the DEM-CHILD patient register was used; this was the basis for the ISE analysis of June 2016. At that time, the register included 69 patients with CLN2 from two centres (Germany and Italy). The patients identified in the database were selected using various filters in order to obtain a patient collective comparable to Study 190-201. After applying the filters, 49 patients who fulfilled the eligibility

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criteria for the historical comparison remained (evaluable population). Of these 49 patients, 7 patients transferred to Study 190-201, thereby reducing the evaluable population to 42 patients.

Pairing criteria were prospectively defined for comparison of the primary endpoint of Study 190-201/190-202 with the historical control study 190-901: There had to be an identical ML/HML value and the smallest possible age difference (but not more than 12 months). A total of 22 of the 23 patients in the ITT population (190-201) and 22 of the "evaluable" patients in the historical control group (190-901) met the criteria for 1:1 pairing. As supportive analyses to 1:1 matching, pairing simulations and a second selection algorithm were used, and "many-to-one pairing" was performed.

Uncertainties of the study

Because of the low certainty of results of a historical comparison, central prerequisites are completeness and a collection method of the underlying data that is as equal as possible, especially with regard to prognostic factors, representativeness, and selection of possible controls. The DEM-CHILD register is the largest database of international CLN2 disease patient data to date. However, it cannot be conclusively assessed to what extent the data available from only two centres (Hamburg and Verona) of the DEM-CHILD register and the selection of the evaluable population of N = 42 patients may have led to selection effects. Furthermore, the HML score in the register was surveyed partly retrospectively and historically–temporally differently from the ML score of Study 201/202. Here, too, it cannot be assessed to what extent this has resulted in biases with regard to the results of the historical comparison.

For the certainty of results of a historical comparison, the completeness of the information and the sufficient agreement of the characteristics of the study populations considered are also essential. Differences between the 42 evaluable register patients and the 23 patients in Studies 190-201/202 exist mainly with regard to the mean age at diagnosis. The sex and genotype distribution between the groups was also not balanced. However, for the three sub-group characteristics age, sex, and genotype, sub-group analyses were subsequently submitted in the written statement procedure; the result showed no effect modification for the characteristics mentioned. A comparison of the study populations considered with regard to concomitant medication, other diseases, and therapies carried out is not possible because no data are available for the patients in the DEM-CHILD register. The extent to which the lack of these data would have a relevant influence on the result of the benefit assessment remains open.

Mortality

No patient died in the Study 190-201. The currently ongoing extension study 190-202 is expected to provide initial results on mortality. The updated analysis on the natural history of the disease based on the DEM-CHILD dataset (190-901) does not include data on overall survival.

Morbidity

M/L scale/ 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

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studies 190-201/190-202 with the developers of the HML scale in order to obtain objective anchor points and clarify the demarcation between categories.

Both the HML scale and the ML scale (0–6 points) include only two domains (motor skills and speech) out of the original total of four domains of the overall 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 increments within both domains describing normal abilities (3 points) to complete loss of function (0 points). The scale captures distinguishable milestones of motor and language skills. For example, the decrease of a score from 2 to 1 in the motor domain is characterised by a change from still being able to walk independently ≥ 10 steps to no longer being able to walk independently. An inclusion criterion for Study 190-201 was a score of 3–6 on the ML scale with an ML score of at least 1 in each of the two domains.

The domains vision and epileptic seizures were not recorded in the ML scale. Although these domains are considered important endpoints in CLN2 disease, in the present case, the use of the motor domain and language domain can be considered sufficient for assessing disease progression. Taking into consideration the natural course of the disease in patients with confirmed CLN2 disease, a preservation or improvement of these motor and language abilities addressed in the ML scale appears to be comprehensible and patient-relevant. However, a methodologically adequate validation of the ML scale is available only to a limited extent.

For the comparison of the efficacy data (ML/HML scale) of Studies 190-201/190-202 with Study 190-901 (Integrated Summary of Efficacy, ISE), the data cut-off of 15 June 2016 is used. The primary endpoint was evaluated as a responder analysis and a slope analysis. The definition of the primary endpoint response of the ISE differs from the responder definition in the single-arm Studies 190-201/202: The response is defined here in terms of slope, i.e. the magnitude of the decrease in motor and language skills measured by means of the event history of the (H)ML values. Responders were thus defined as patients in whom the decrease (slope of the line), scaled to 48 weeks, was less than two (< 2). In addition, the time from baseline to the first stable decrease of ≥ 2 points on the ML/HML scale or the time to a value of zero was also analysed as a time-to-event analysis using the Kaplan-Meier method.

Results

Responder analysis: The proportion of patients in whom the decrease scaled to 48 weeks was less than two was 100% (n = 22/22) in patients treated with cerliponase alpha compared with 45% (n = 10/22) of patients in the historical control group. The difference is statistically significant in favour of treatment with cerliponase alfa (p = 0.0009).

Slope analysis: The ML/HML score, scaled to 48 weeks, fell by a mean of 2.0 points in patients of Study 190-901 compared with 0.34 points for the patients in Study 190-201/202 – a difference of 1.66 points (p < 0.0001) scaled to 48 weeks.

Time-to-event analysis: For the time-to-event analysis defined in the ISE SAP, the most recent data from 1 November 2016 (N = 21 pairs) are used in addition to the data from the data cut-off of 15 June 2016 (N = 22 pairs). The hazard ratio (HR) was 0.10 ([95% CI 0.03; 0.38], p = 0.0005) for an observation time up to 72 weeks. There is thus a relative risk reduction of disease progression as measured by the linear estimated decrease of the ML scale of 90% for patients on cerliponase alfa compared with historical control patients. The median time to disease progression in historical control patients was 285 days (95% CI: 210; 420); the median in treatment-naive patients has not yet been reached.

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The results of the sensitivity and supportive analyses for the primary endpoint indicate that the effects are similar to those of the main analysis.

Uncertainties related to data collection in the historical control cohort come into play in the analysis for the primary endpoint. For the measurement of motor and language skills, different scale variants (ML scale and HML scale) were used in the study population (190-201/190-202) and the control cohort (190-901); the validity and comparability of these have not been conclusively proven. For the HML baseline scores from Study 190-901, it is also not clear to what extent they were measured directly or determined retrospectively. In addition, the retrospective determination was based on the memory of the patients' relatives. The measured or determined HML baseline scores were used to calculate the estimated progression rate, which is intended to represent the natural history of the disease. The extent to which retrospectively collected estimates have a biasing effect and the annual decrease of 2 points on the HML scale defined as a threshold value represent an overestimation of natural decrease cannot be determined with certainty.

However, there are no indications that the possible bias resulting from retrospective data collection has had an effect in only one direction (over- or underestimation).

As a result, the size and consistency of the differences in the changes of the M/L scale/HML scale show an extraordinarily clear effect of treatment with cerliponase alfa compared with the untreated control; this is not called into question by the uncertainties mentioned.

Further morbidity data from Study 201/202

The morbidity data surveyed only in Study 190-201/202 refer to responder rate (defined as a net decrease of < 2 by Week 48) and data of the MLV/MLVS scale. At both Week 48 and Week 80, the responder rate remained unchanged at 87%.

The modified MLV scale (0–9 points) consists of three domains: motor skills, speech, and vision; the modified MLVS scale (0–12 points) consists of four domains: motor skills, speech, vision, and epileptic seizures. The additional domains of vision and epileptic seizures collected in the MLV and MLVS compared with the HML/ML scale are considered relevant to the patient. However, there is a lack of information on the validity of these scales. Against this background and taking into consideration that the use of the motor domain and speech domain is assessed as sufficient for the assessment of disease progression, the results of the domains vision and epileptic seizures within the survey instruments MLV/MLVS scale are presented additionally. For the ML, MLV, and MLVS scales, data up to treatment week 97 were submitted in the written statement procedure. Compared with the data at treatment week 73, there remains a slight deterioration in the values of the ML scale and MLV scale, while the values of the MLVS scale remain almost unchanged compared to the baseline values.

Quality of life

No comparative data on quality of life are available for the benefit assessment.

PedsQL

The PedsQL is an established, generic instrument for assessing quality of life in paediatric populations with chronic diseases. Within Studies 190-201/202, the parent version was used for children between 2 and 4 years of age regardless of the age of the children. The PedsQL is considered valid for the assessment of patient-relevant quality of life. For Study 190-201,

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PedsQL data in the ITT population (N = 23) showed an average improvement in total score of 2.6 points from study baseline to the last observation in the study (Week 49). Only in the dimension “physical competencies” was there a deterioration at the end of the study compared with the baseline values (mean of 6.1 points). In extension study 190-202, there was a deterioration in all dimensions compared with the baseline values of the overall study (week 98). Thus, the total score decreased by a mean of 14.1 points, and physical competence decreased by a mean of 27.9 points by week 98. However, for week 98, data are available from only 12 of the 23 patients.

CLN2-specific QoL

The CLN2-specific QoL questionnaire is not considered in this benefit assessment. There is a lack of information from the pharmaceutical company regarding the development and validation, which is why a conclusive assessment of the suitability and validity of the questionnaire is not possible.

Side effects

No comparative data on side effects are available for the benefit assessment.

Information on long-term effects is available up to the data cut-off of 3 June 2016 with a median treatment duration of 95 weeks. In the study, there were no discontinuations because of AE and no deaths. A total of 51 SAEs were recorded in 79% of patients, and AEs of NCI-CTCAE grade 3 and higher were recorded in 54% of patients. An estimation of the frequency of adverse events is limited because of the lack of a control group. The most common (> 20%) side effects observed included fever, decreased CSF protein, ECG abnormalities, vomiting, upper respiratory tract infections, and hypersensitivity reactions. No patient had to discontinue treatment because of adverse events.

<u>Overall assessment:</u>

The consideration of the historical comparison seems justified on the basis of the very rare disease, the paediatric patient population, and the deterministic course of the disease.

The results of the historical comparison show statistically significant effects in favour of cerliponase alfa in the category of morbidity for the analyses of the ML scale with regard to the preservation of patient-relevant motor and linguistic abilities, which are extraordinarily pronounced. However, there are the aforementioned uncertainties regarding the historical comparison cohort and the primary endpoint. However, the possibility that a bias caused by the uncertainties is solely responsible for the large differences observed in the changes in the ML/HML scale in favour of cerliponase alfa can almost be ruled out.

No comparable data are available for the quality of life and side effects category. No improvement in quality of life was observed during treatment with cerliponase alfa. However, in the present disease, for which therapy success is defined by the absence or slowing of disease progression, it cannot necessarily be assumed that the quality of life of the patients will improve. In the overall consideration, with cerliponase alfa treatment, there was no overall change in quality of life at Week 48; however there was a deterioration at Week 98. The “physical competencies” in the benefit category quality of life deteriorated over the course of 48 weeks and indicate a further deterioration after 98 weeks. How this result is to be evaluated and related to the opposite findings of motor skills and language ability in the benefit category

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morbidity remains questionable, especially because of the lack of comparative quality of life data within the historical control cohort.

Because there are no data on adverse events in the historical control cohort, a comparison with the previous symptomatic therapy approach in the presence of neuronal ceroid lipofuscinosis type 2 is not possible. From the perspective of a comparative benefit assessment, the side effect profile cannot be assessed with certainty because of the lack of comparative data and the short observation period of Study 190-201/202 for a therapy tested in humans for the first time. Further long-term data are necessary for the assessment of side effects.

Because of the uncertainties mentioned, a proper assessment of the extent of the additional benefit of cerliponase alfa is not possible with any degree of certainty.

Summary:

The pivotal intervention study (190-201) as well as its extension study (190-202) and the study for historical comparison (190-901) were used to assess the additional benefit. In the primary endpoint, there are clear advantages for cerliponase alfa with respect to the preservation of patient-relevant motor and language abilities compared with a predictable, rapidly progressive loss of these abilities in the natural disease course of neuronal ceroid lipofuscinosis Type 2. The uncertainties of this historical comparison and the limited validation of the survey instrument must be considered. At the same time, because of the lack of comparative data (or data that can be assessed only to a limited extent) on the quality of life and the safety profile of cerliponase alfa, there are relevant uncertainties that do not allow a conclusive estimate of the extent of the therapy-relevant benefit of cerliponase alfa based on the scientific data currently available.

In summary, the G-BA recognises an additional benefit of cerliponase alfa on the basis of the criteria in Section 5, paragraph 7 AM-NutzenV, taking into consideration the severity of the disease and the therapeutic objective; however the extent of this additional benefit is non-quantifiable.

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 cerliponase alfa has 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 this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V. On one hand, these result from the conditions associated with marketing authorisation under “exceptional circumstances”: A non-interventional post-authorisation safety study (PASS) to assess the long-term safety resulting from a registration of patients with CLN2 (register study). Furthermore, a non-interventional post-authorisation efficacy study (PAES) is being conducted to assess disease progression using the motor and language scale as well as safety and tolerability. The results are expected in 2020. On the other hand, in order to obtain further scientific evidence as a prerequisite for a sufficiently reliable assessment of the extent of the additional benefit of cerliponase alfa with regard to the influence of patient-relevant endpoints (mortality, morbidity, quality of life, and side effects), the G-BA considers it necessary for the pharmaceutical

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company to record data for the patients in Germany treated with cerliponase alfa in a clinical register. In this way, representative data on patient-relevant endpoints will be generated for the German health care context. A complete survey of data from all patients should be sought. Collection of such data also serves the purpose of benefit assessments according to Section 35a paragraph 1 SGB V, namely to create a basis for the determination of requirements for quality-assured application of the medicinal product and, thus, to ensure the medicinal product is prescribed in a cost-effective manner.

At the end of the time limit, data from the register and the final data of study 190-202 as well as data from the requirements of the EMA are to be submitted to the G-BA in order to enable a more reliable assessment of the extent of additional benefit with respect to patient-relevant endpoints (mortality, morbidity, quality of life, and side effects) and on the basis of long-term therapy with cerliponase alfa.

An extension of the deadline until 1 June 2021 is considered appropriate for this purpose.

The pharmaceutical company may request consultation on the specific requirements of the G-BA regarding the data to be submitted by the deadline and on the design of the register in accordance with Chapter 5, Section 7 VerfO of the G-BA.

In accordance with Section 3, number 5 AM-NutzenV and in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of cerliponase alfa shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of cerliponase alfa (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment of cerliponase alfa can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2 VerfO) remains unaffected by this.

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 resolution is based on the information from the dossier of the pharmaceutical company and the assessment of the IQWiG (Order G-17-06). The data on the prevalence of neuronal ceroid lipofuscinosis Type 2 are based on a retrospective survey in West Germany with a return rate of between 65 and 85%[2]. Based on the cumulative number of cases and the number of live births between 1968 and 1977, the incidence rate of 0.46 per 100 000 live births was calculated. The calculation is uncertain because of the lack of up-to-date data and the possibility that diagnostic options have changed. Using the incidence rate and median age at death according to as yet unpublished data from the DEM Child Register[3], the prevalence is estimated at 33 patients with CLN2. Based on the proportion of SHI-insured persons in the German resident population (86.5%), a case number of the target population of 26 SHI patients (19–37 patients) is determined.

Overall, the order of magnitude seems plausible despite uncertainties.

2 Claussen M, Heim P, Knispel J, Goebel HH, Kohlschütter A. Incidence of neuronal ceroid-lipofuscinoses in West Germany: variation of a method for studying autosomal recessive disorders. Am J Med Genet 1992; 42(4): 536–538.
3 Nickel M, Simonati A, Jacoby D, Lezius S, Down M, Genter F et al. Natural History of CLN2 disease: quantitative assessment of disease characteristics and rate of progression in an international cohort of 137 patients [Manuskript]. 2016.

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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: 8 November 2017):

http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/004065/WC500229798.pdf

Treatment with cerliponase alfa as well as the administration of cerliponase alfa may be initiated and monitored only by specialists who are experienced in the intracerebroventricular administration of medicinal products.

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will assess new information on this medicinal product at a minimum once per year and update the product information where necessary.

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: 1 December 2017).

In order to improve comparability, the costs of the medicinal products were approximated based on the pharmacy sales price level as well as less the statutory rebates according to Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

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

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration/treatment (days)	Treatment days per patient per year
Cerliponase alfa	Every 2 weeks	26	1	26

Usage and consumption:

Designation of the therapy	Potency	Dose per patient per treatment day	Consumption by potency per treatment day	Treatment days per patient per year	Average annual consumption by potency

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Cerliponase alfa	150 mg	300 mg	2 × 150mg	26	52 vials with 150mg

Costs:

Costs of the medicinal product:

Designation of the therapy	Costs (pharmacy sales price according to potency and package size)	Costs after deduction of statutory rebates
Cerliponase alfa	€ 30,471.71 150 mg, 2 vials	€ 28,732.97 [€ 1.77[4]; € 1,736.97[5]]

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 December 2017

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 costs for the necessary medical treatment or the prescription of other services when using 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 standard expenditure in the course of the treatment are not shown.

Implantation of an intracerebroventricular access device is done once before starting 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.

Type of service	Cost per treatment	Costs per patient per year
Implantation of an intracerebro-ventricular access device, infusion, laboratory examination of the cerebrospinal fluid	Non-quantifiable	Non-quantifiable

4 Rebate according to Section 130 SGB V
5 Rebate according to Section 130a SGB V

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3. Bureaucratic costs

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 2017, 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, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 2 October 2017 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 23 October 2017.

The oral hearing was held on 6 November 2017.

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 were discussed at the session of the subcommittee on 12 December 2017, and the proposed resolution was approved.

At its session on 21 December 2017, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 September 2017	Information of the benefit assessment of the G-BA
Working group Section 35a	1 November 2017	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	6 November 2017	Conduct of the oral hearing
Working group Section 35a	15 November 2017 29 November 2017 5 December 2017	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 on Medicinal Products	12 December 2017	Concluding discussion of the draft resolution
Plenum	21 December 2017	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Courtesy translation – only the German version is legally binding.

Berlin, 21 December 2017

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

Courtesy translation – only the German version is legally binding.