Justification

Gemeinsamer Bundesausschuss

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

of 19 December 2019

Contents

1. Legal basis

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

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

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 in such a way 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient pegvaliase in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 July 2019. 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 28 June 2019.

Pegvaliase for the treatment of phenylketonuria is approved as a medicinal product for the treatment of a rare disease in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be already proven by 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 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 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de) on 1 October 2019, 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 G19-12) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

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

In the light of the above and taking into account the 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 pegvaliase (Palynziq®) in accordance with product information

Pegvaliase is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/l) despite prior management with available treatment options.

2.1.2 Extent of the additional benefit indicating the significance of the evidence

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

For patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/l), there is a

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.

hint for a non-quantifiable additional benefit for pegvaliase because the scientific data basis does not allow quantification.

Justification:

The pharmaceutical company submits the two pivotal studies 165-301 and 165-302 for the benefit assessment.

Study 165-301 is an uncontrolled study in which different doses of the active ingredient pegvaliase were compared during an induction, a titration, and a maintenance phase. A total of 261 patients with phenylketonuria were randomised to two intervention arms – pegvaliase at a target dose of 20 mg/day or a target dose of 40 mg/day.
The total duration of the study was between 26 and 36 weeks. After completion of the study, patients could be included in Study 165-302. If the patients reached low phenylalanine levels because of a rapid decline and had received the target dose for at least 2 weeks, they were included in Study 165-302 at the discretion of the study personnel and medical monitors even before the completion of 26 weeks. The primary endpoint of the study was the safety and tolerability of pegvaliase, other endpoints included phenylalanine (Phe) concentration in the blood or protein intake from natural and medical foods. Study165-301 was conducted in the US between May 2013 and the end of 2015.

Study 165-302 is a Phase III study consisting of four different study sections. The study included patients who had previously completed one of several studies on pegvaliase. Most patients included in the study had previously participated in Study 165-301 (n = 203; 94.4%); the other patients had previously participated in one of the Phase II studies.
In study section 1, patients (n = 164) received up to 13 weeks of pegvaliase without blinding at the same dose (20 or 40 mg/day) as in the previous study.
In accordance with an amendment to the study protocol, only patients with at least a 20% reduction in Phe concentration since baseline in the previous study should be included in study section 2 (9 patients were included before the amendment and do not meet this criterion). If such a reduction had not occurred after 13 weeks, the patients proceeded directly to study section 4.
In study section 2 the patients (n = 95) received either pegvaliase or placebo for a period of 8 weeks according to randomisation. Study participants who received pegvaliase at a dose of 20 mg/day in study section 1 were randomised 2:1 to 20 mg/day pegvaliase or an equivalent placebo (low dose placebo). Study participants who received pegvaliase at a dose of 40 mg/day in study section 1 were randomised 2:1 to 40 mg/day pegvaliase or an equivalent placebo (high dose placebo).
In study section, 3 the patients (n = 89) received pegvaliase for 5 weeks in the same dosage as in study section 1; in week 6 no study medication was administered. Pharmacokinetic and pharmacodynamic investigations were performed in weeks 1 and 6.
In study section 4, all patients (n = 202) received pegvaliase in an open long-term extension of up to 274 weeks.
The study has been conducted in the USA since July 2013. Study section 4 is not yet completed.

Study section 4 is a one-armed long-term extension without control arm. The pharmaceutical company uses data from a product-related register to perform a historical comparison exclusively for the Phe concentration in blood. Because the registry data allow only a non-adjusted indirect comparison with the data on Phe concentration in blood and are subject to considerable uncertainties, the data of the registry are not considered for the benefit assessment.

Mortality

Deaths were recorded as part of the recording of adverse events.

In Study 165-301 a death for which there is no connection to the administration of the study medication occurred. The study participant died of an electric shock.

No deaths occurred in the course of Study 165-302.

No statements on the extent of the additional benefit can be derived from the data on mortality.

Morbidity

Phenylalanine concentration (*Phe concentration) in the blood*

In the present therapeutic indication, the concentration of Phe in the blood is a clinically relevant parameter used for diagnosis and therapy control. Current guidelines[2] recommend permanent treatment (diet and, if necessary, sapropterin) in patients with phenylketonuria and an (untreated) blood Phe concentration of > 600 µmol/l or of > 360 µmol/l (especially in children up to 12 years and pregnant women). Also taking into account the patient-individual clinical manifestation and the limited evidence for the threshold value in adult patients, the reduction of the blood Phe concentration below the threshold values in the present therapeutic indication represents a clinical goal in the treatment of patients with phenylketonuria. Furthermore, however, the significance of a certain change in blood Phe concentration on the patient-individual symptomatology is unclear.

In Study 165-301, after week 20, the blood Phe concentration is reduced on average by 403.7 µmol/l to a mean value of 807.5 µmol/l compared with baseline. From week 24 onwards, the proportion of patients for whom information on phenyl concentration is available is less than 70% of the study population. For this reason, the results are not presented.

In Study 165-302, the mean Phe concentration in the blood during the 8-week discontinuation trial in study section 2 increased to a significantly lower extent when the respective dose of pegvaliase was administered or when the respective placebo was administered – both for the low dose of 20 mg/day and for the higher dose of 40 mg/day.

The data on mean blood Phe concentration in study section 4 (uncontrolled long-term extension) of Study 165-302 are not presented because the calculated return rate at all measurement points during study section 4 of Study 165-302 is < 70%. To calculate the return rate, all patients for whom baseline Phe concentrations in blood were to be determined in Study 165-301 or in one of the Phase 2 studies and who were basically eligible for inclusion in Study 165-302 were used.

Natural protein intake

Long-term adherence to a strict phenylalanine-restricted diet with the intake of synthetic amino acid mixtures (to prevent malnutrition) is currently the mainstay of phenylketonuria therapy. The reduction of phenylalanine levels below the limit values with simultaneous normalised natural protein intake can therefore be considered a therapeutic goal in the present therapeutic indication.

The operationalisation of the endpoint “natural protein intake” within studies 165-301 and 165-302 does not allow any statement on whether pegvaliase enables a normal or improved

2 e.g. Van Spronsen FJ, van Wegberg AM, Ahring K, Belanger-Quintana A, Blau N, Bosch AM, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol 2017;5(9): 743–756.

natural protein intake while lowering the Phe concentration in the blood. In accordance with the study protocol, the respective protein intake of the patients should be maintained throughout the entire duration of the study. This was considered to be fulfilled if the protein intake from both natural and medical food sources changed by less than 10%. A change in protein intake was planned only if the blood Phe concentration dropped to 30 µmol/l or lower. In addition, a change (increase) in the intake of natural protein should be made only if the respective patient has previously consumed less or less than twice the amount of natural protein recommended by the RDA (recommended dietary allowance).

No information could be identified on the number of patients in whom protein intake was adjusted within studies 165-301 and 165-302 because of low phenylalanine levels in the blood (≤ 30 µmol/l).

The data of the endpoint “natural protein intake” are not presented in the benefit assessment because of the lack of significance.

PKU-POMS

The PKU-POMS is based on the instrument “Profile of Mood States” (POMS) and was developed by the pharmaceutical company with the participation of affected persons to assess mood swings in adults with PKU. The questionnaire consists of 20 adjectives assigned to the six sub-scales of anxiety, depression, anger, activity, fatigue, and confusion.

The PKU-POMS-TMD (Total Mood Disturbance) covers a score range from −12 (best possible value) to 58 points (worst possible value). The confusion sub-scale covers a range of 0–12 points, where a value of 0 corresponds to no confusion and a value of 12 to great confusion.

The data of the PKU-POMS are subject to uncertainties because the results of Study 165-301 were simultaneously used for the development and validation of the PKU-POMS. Furthermore, in both studies, no separate item-reduced PKU-POMS questionnaire was used. Instead, the entire POMS questionnaire and a subset of the answered items were used to determine the PKU-POMS.

The significance of the results is severely limited because of the methodological uncertainties described above. The endpoint is therefore not considered relevant for evaluation.

ADHD-RS-IV

The ADHD-RS-IV (attention deficit/hyperactivity disorder rating scale) is an instrument for external assessment of inattention and hyperactivity symptoms, which was primarily developed for the diagnosis of ADHD in children and adolescents. The instrument includes the sub-scales inattention and hyperactivity. Both sub-scales each contain 9 items that are rated on a 4-point Likert scale (0 = never or rarely/1 = sometimes/2 = often/3 = very often). The sub-scales can assume values in the range from 0 (no impairment) to 27 (maximum impairment).

Investigations of the psychometric characteristics of ADHD-RS-IV are only available for children with PKU; investigations with adult patients with PKU could not be identified. Furthermore, based on the existing baseline characteristics of Study 165-301, it is not evident that the patients in the studies would not have been able to perform a self-

assessment. Because the ADHD also exists in a self-assessment version, it remains unclear why the third-party assessment version of the ADHD was used in the studies.

The significance of the results is severely limited because of the methodological uncertainties described above. The endpoint is therefore not considered relevant for evaluation.

No statements on the extent of the additional benefit can be derived from the data on morbidity.

Quality of life

Health-related quality of life data have not been submitted.

Side effects

In studies 165-301 and 165-302, almost all patients suffered an adverse event (AE).

In Study 165-301, 29 patients (11.1%) had an AE that led to discontinuation of the study medication. The most frequent of these AEs in relation to preferred term were “anaphylactic reactions” (n = 6; 2.3%) and “arthralgia” (n = 6; 2.3%). All other events resulted in less than 2% of the study population discontinuing the study medication. In addition, 39 patients (14.9%) had at least one AE of severity 3 or higher. In Study 165-301, immune system disorders with severity 3 or higher occurred in 16 patients (6.1%). No other AE of severity ≥ 3 occurred in more than 5% of patients in accordance with system organ class or preferred term.

In Study 165-301 at least one SAE occurred in 26 patients (10.0%). SAE in immune system disorders occurred in 14 patients (5.4%). No other SAE occurred in more than 5% of patients in accordance with system organ class and preferred term.

In Study 165-302, 12 study participants (5.6%) suffered an AE that led to discontinuation of the study medication. However, an assignment to a preferred term is not possible here. In addition, 30 patients (14.0%) had at least one AE of severity 3 or higher. No AE of severity ≥ 3 occurred in more than 5% of patients in accordance with system organ class or preferred term.

In Study 165-302 at least one SAE occurred in 26 patients (12.1%). SAE in the area of psychiatric disorders occurred in 2 patients (6.3%) treated with 40 mg/day of pegvaliase during Study section 2 of Study 165-302. No other SAE occurred in more than 5% of patients in accordance with system organ class and preferred term.

Anaphylaxis in accordance with NIAID/FAAN criteria (defined as AE of special interest) occurred in 18 patients (6.9%) in Study 165-301 and in 11 patients (5.1%) in Study 165-302. Only in 4 patients (1.5%) in Study 165-301 did these events meet Brown’s criteria for a severe event.

Because the majority of patients in Study 165-301 subsequently participated in Study 165-302, patients who suffered an AE in Study 165-302 may have already suffered an AE in Study 165-301. The number of patients to whom this applies is unclear.

For the comparisons during study section 2 (20 mg/day pegvaliase vs “low dose placebo”; 40 mg/day pegvaliase vs “high dose placebo”) of Study 165-302, no effect estimators and p values were presented.

No statements on the extent of the additional benefit can be derived from the data on side effects.

Overall assessment

For the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/l) despite prior management with available treatment options, results on mortality, morbidity, and adverse events are available based on the pivotal authorisation studies 165-301 and 165-302.

No statements on the extent of the additional benefit can be derived from the data on mortality.

In the morbidity category, a statistically significant change in blood Phe concentration in favour of treatment with pegvaliase compared with placebo after 8 weeks and a reduction in blood Phe concentration compared with baseline over a period of 20 weeks was shown. The laboratory parameter has a clinical relevance in the diagnosis and follow-up of the disease. However, the additional significance of a certain change in the Phe concentration in the blood on the patient-individual symptomatology is unclear.
For the endpoint category morbidity, no statements on the extent of the additional benefit can be derived based on the data presented.

For quality of life, there are no data for the benefit assessment.
No statements on the extent of the additional benefit can be derived from the data on side effects.

In summary, the present results are classified as non-quantifiable in their extent because the scientific data basis does not allow quantification.

Significance of the evidence

Study 165-301 and Study 165-302 (except study section 2) do not include a control arm; a high risk of bias can therefore be assumed. There are no usable indirect comparisons

The data of study section 2 are subject to considerable uncertainties and make the transferability to clinical practice appear doubtful. A study duration of 8 weeks is too short to obtain significant comparative data on the efficacy and safety of pegvaliase compared with placebo. In addition, most of the patients included in study section 2 showed a ≥ 20% reduction of the Phe concentration compared with the baseline of the previous study. Accordingly, in study section 2, a selective patient population of the study population of Study 165-302 was examined. In addition, patients who had discontinued Study 165-301 (e.g. because of AE or at their own request) were not included in Study 165-302 and thus not in study section 2. Because of a missing washout phase, it also remains unclear to what extent the previous treatment with pegvaliase led to carry-over effects on the data collected within the control group (placebo).

In the overall view, there is a hint for a non-quantifiable additional benefit in terms of the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product “Palynziq®” with the active ingredient pegvaliase. Pegvaliase is approved for the treatment of patients with phenylketonuria aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/l) despite prior management with available treatment options.

For the benefit assessment, the pharmaceutical company submits the two Phase III registration studies 165-301 (uncontrolled study) and 165-302. Study 165-302 is divided into 4 study sections; study section 2 is a randomised, placebo-controlled, double-blind discontinuation trial.

No statements on the extent of the additional benefit can be derived from the data on mortality.

In the morbidity category, for the primary endpoint “Phe concentration in blood”, a statistically significant change in blood Phe concentration in favour of treatment with pegvaliase compared with placebo after 8 weeks and a reduction in blood Phe concentration compared with baseline over a period of 20 weeks was shown. The parameter has a clinical relevance in the diagnosis and follow-up of the disease. However, the additional significance of a certain change in the Phe concentration in the blood on the patient-individual symptomatology is unclear. No statements on the extent of the additional benefit can be derived from the data on morbidity.
For quality of life, there are no data for the benefit assessment.
No statements on the extent of the additional benefit can be derived from the data on side effects.
The significance of the two studies presented is classified as limited. On the one hand, this is due to a high risk of bias in studies without control arm. Furthermore, because of a comparative study duration of only 8 weeks, a selective patient population, and possible carry-over effects from previous treatment with pegvaliase, there are considerable uncertainties regarding the data from study section 2 of Study 165-302; these therefore cast doubt on the transferability to clinical practice.
In the overall view, for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/l), there is a hint for a non-quantifiable additional benefit for because the scientific data basis does not allow quantification.

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 the resolution on the number stated by the pharmaceutical company in the dossier. The IQWIG estimates this number to be uncertain.
To estimate the number of patients from 16 years of age with phenylketonuria in Germany in 2019, the pharmaceutical company takes into account data from the Federal Statistical Office on the number of live births in Germany from 1970 to the first half of 2003 under the assumption that patients born before 1970 are therapy-naïve (newborn screening was introduced in 1969). However, it is uncertain whether the corresponding adult patients are actually not in treatment under the current medical treatment situation. There is thus a potential underestimation of the number of patients.
The proportion of patients cared for in clinics estimated by the pharmaceutical company is also uncertain based on the questionable transferability to the German healthcare context because the pharmaceutical company derives the estimate from data for the US and the

Netherlands. There are also uncertainties regarding the transferability of the proportion of patients with a blood phenylalanine concentration of more than 600 µmol/l based on data from a special outpatient clinic in Leipzig.
In addition, the proportion of patients with phenylketonuria treated with sapropterin deducted from the target population by the pharmaceutical company based on data from a routine data analysis appears to be too high. It is also unclear to what extent all patients treated with sapropterin reach a blood phenylalanine concentration of less than 600 µmol/l and thus no longer correspond to the target population.
Overall, the number of patients in the SHI target population stated by the pharmaceutical company appears to be underestimated.

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 Palynziq® (active ingredient: pegvaliase) at the following publicly accessible link (last access: 7 November 2019):

https://www.ema.europa.eu/documents/product-information/palynziq-epar-product-information_de.pdf

Treatment with pegvaliase should be initiated and monitored only by physicians who are experienced in the treatment of patients with phenylketonuria.

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 2019).

In general, initial induction schemes are not taken into account for the cost representation because 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.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Pegvaliase	continuously, 1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/ treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency

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					
Pegvaliase	20 mg – 60 mg	20 mg – 60 mg	1 – 3 × 20 mg	365	365 – 1,095 × 20 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 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.

Costs of the medicinal product:

Designation of the therapy	Package 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					
Pegvaliase 20 mg	10 SFI	€ 4,960.12	€ 1.77	€ 280.00	€ 4,678.35
Abbreviation: SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 December 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary 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.

Before starting treatment, the phenylalanine level in the blood must be determined. Monitoring of the phenylalanine level in the blood is recommended at intervals of one month

According to product information, during treatment with Palynziq, patients should always carry an adrenaline injection product with them.

Designation of the therapy	Description of the service	Costs per application		Number per year
Medicinal product to be assessed				
Pegvaliase	Measurement of the phenylalanine level in the blood	Quantitative chemical or physical determination GOP 32235	€ 9.20	12
	Adrenaline injection product	Epinephrine 1 prefabricated pen	€ 83.61	different for each individual patient

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 28 June 2019, the pharmaceutical company submitted a dossier for the benefit assessment of pegvaliase 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 1 October 2019 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 22 October 2019.

The oral hearing was held on 11 November 2019.

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 10 December 2019, and the proposed resolution was approved.

At its session on 19 December 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	24 September 2019	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	5 November 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	11 November 2019	Conduct of the oral hearing
Working group Section 35a	19 November 2019 3 December 2019	Consultation on the dossier evaluation 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	10 December 2019	Concluding discussion of the proposed resolution
Plenum	19 December 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 19 December 2019

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

Prof. Hecken