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)
Cipaglucosidase alfa (Pompe disease, combination with miglustat)

of 1 February 2024

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient cipaglucosidase alfa on 1 August 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 1 August 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 November 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of cipaglucosidase alfa compared with the appropriate comparator therapy could be determined on the basis of the

dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of cipaglucosidase alfa.

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

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Cipaglucosidase alfa (Pombiliti) according to the product information

Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

Therapeutic indication of the resolution (resolution of 1 February 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)

Appropriate comparator therapy for cipaglucosidase alfa in combination with miglustat:

Alglucosidase alfa

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

on 1. In addition to cipaglucosidase alfa, alglucosidase alfa is also approved for this therapeutic indication.

on 2. Non-medical measures within the meaning of the Remedies Directive (e.g. physiotherapy, voice, speech and language therapy, occupational therapy) can be considered in the present indication.

on 3. To date, no resolutions have been made by the G-BA on the benefit assessment according to Section 35a SGB V in the present indication.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a, paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

The evidence for the present therapeutic indication is very limited. No Cochrane reviews could be included in the evidence synopsis. One systematic review could be considered and, in the absence of higher-quality evidence, the guideline Van der Ploeg AT et al, 2017 was used as a supplement for this indication.

Based on the available evidence, treatment with alglucosidase alfa is an established therapy standard in this therapeutic indication "for the long-term treatment of adult patients with Pompe disease".

Consequently, for cipaglucosidase alfa/ miglustat, the active ingredient alglucosidase alfa is determined as the appropriate comparator therapy in the present indication.

In addition, the available evidence contains recommendations for non-medicinal measures as defined by the Remedies Directive (e.g. physiotherapy, voice, speech and language therapy, occupational therapy). Physiotherapy measures should be made available to patients in both arms of the study if indicated.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

Hint for a minor additional benefit

Justification:

The pharmaceutical company submits the results of the PROPEL study. This is a double-blind, randomised study with the treatment arms cipaglucosidase alfa (20 mg/kg every 2 weeks) plus miglustat (weight-related 195 or 260 mg) (n = 85) and alglucosidase alfa (20 mg/kg every 2 weeks) plus placebo (n = 38), which was conducted in 62 study sites worldwide.

Adult patients aged 18 years and older with a genotyping-confirmed diagnosis of LOPD, a body weight ≥ 40 kg, a seated forced vital capacity (FVC) ≥ 30% of the predicted healthy adult value and two 6-minute walk tests (6MWT), where the distance travelled had to be ≥ 75 m and ≤ 90% of the predicted healthy adult value (based on sex, age, height and weight) were enrolled. Patients who required invasive or non-invasive respiratory support for > 6 hours per day while awake were excluded from participation in the study. The randomisation was stratified according to the distance travelled in the 6MWT at the start of study and the pretreatment (enzyme replacement therapy-naive vs pretreated). The treatments were carried out over 52 weeks in accordance with the respective product information. Pretreatment with alglucosidase alfa was permitted and had taken place in about 80% of the study participants.

The pharmaceutical company presents responder analyses for some of the patient-relevant endpoints (physical resilience using 6MWT, health status using EQ-5D VAS, motor function using GSGC) for the evaluation period up to week 52, but these were not used to assess the additional benefit, as the evaluations at week 52 are relevant in this therapeutic indication.

Extent and probability of the additional benefit

Mortality

There were no deaths in the studies.

Morbidity

Physical functioning using R-PAct

The Rasch-built Pompe-specific activity (R-PAct) instrument is a patient-reported questionnaire to measure the impact of Pompe disease on activities of daily living and social participation. The questionnaire consists of 18 items and is considered validated for the present indication. For the benefit assessment, the data subsequently submitted by the pharmaceutical company in the written statement procedure are taken into account, in which an adequate transformation of the data to a scale range of 0 to 100 was performed. In this indication, the responder analyses for deterioration at the evaluation time point of week 52 are relevant. The response threshold for deterioration was defined as a decrease by 15% of the scale range, i.e. by ≥ 15 points compared to the start of study. There is a high percentage of missing values (27.1% in the cipaglucosidase alfa arm and 15.8% in the alglucosidase alfa arm), which the pharmaceutical company replaced using an imputation procedure; the results can be used for assessment of the additional benefit. As a result, only one subject from the treatment arm with cipglucosidase alfa and no subjects from the comparator arm reached this threshold, meaning that no relevant difference can be derived for the benefit assessment.

Physical functioning, fatigue, dyspnoea, function of the upper extremities using PROMIS

PROMIS (Patient Reported Outcome Measurement Information System) is a generic system of different instruments for the assessment of physical, mental and social health. The patient-reported questionnaires PROMIS Physical Function Short Form 20a, PROMIS Fatigue Short Form 8a, PROMIS Dyspnoea Severity Short Form 10a and PROMIS Upper Extremity Short Form 7a were used in the study. The selection of these instruments is considered adequate for the present indication.

For the benefit assessment, the data subsequently submitted by the pharmaceutical company in the written statement procedure are taken into account, in which a transformation of the data was carried out according to the conversion tables of the corresponding PROMIS manuals. In this approach, patients with missing values cannot be included in the evaluation, which is why the pharmaceutical company replaced the missing values using an imputation procedure. In the questionnaires on physical functioning, fatigue and limb function, the percentage of substituted values is 7 to 30%; the results can be used for assessment of the additional benefit. For the endpoint dyspnoea, there are approx. 60% missing values, which is why the results are unsuitable for the evaluation and are not taken into account.

In this indication, the responder analyses for deterioration at the evaluation time point of week 52 are relevant. The response threshold for deterioration was defined as a decrease by

15% of the respective scale range compared to the start of study. In the endpoint of physical functioning, no subject from the treatment arm with cipglucosidase alfa and only one subject from the comparator arm reached this threshold, so that no relevant difference for the benefit assessment can be derived. There were no statistically significant differences in the results for the endpoints fatigue and function of the upper extremities.

Endpoints collected using SGIC

Changes in general physical well-being, breathing effort, muscle power, muscle function, ability to move, activities of daily living, energy levels and muscle pain were assessed using *Subject's Global Impression of Change* (SGIC). This is a single question that the study participants answer using a 7-point scale. The study participants assessed the change at week 52 compared to the start of the study medication. In the present indication, the responder analyses for deterioration (defined as slightly deteriorated, severely deteriorated or very severely deteriorated) are relevant.

For the endpoints ability to move and energy level, the responder analyses showed statistically significant differences to the advantage of cipaglucosidase alfa plus miglustat.

Physical resilience (6MWT)

Walking ability and physical resilience were assessed using the 6-minute walk test (6MWT). The assessment is not based on the submitted responder analyses (response criterion 15% of the scale range) for the evaluation period up to week 52, but on the mean difference of the change at week 52. There is no statistically significant difference between the treatment arms.

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The assessment is not based on the responder analyses submitted for the evaluation period up to week 52, but on the mean difference of the change at week 52. There is no statistically significant difference between the treatment arms.

Motor function (GSGC)

The GSGC test combines the four motor function tests gait (Gait [G]), stair climbing (Stairs [S]), Gowers manoeuvre (getting up from a lying position, G) and getting up from a chair (Chair [C]), each of which was qualitatively assessed by trained personnel using a 7-point scale (or 6-point for C). To assess the additional benefit, the individual test results and the added total value are considered.

For the total value, there was a statistically significant difference to the advantage of cipaglucosidase alfa plus miglustat over alglucosidase alfa. However, the 95% confidence interval of the standardised mean difference does not indicate that this is a relevant effect.

In addition, the time taken by the patient to complete the individual tests was measured and the time-up-and-go test (TUG) was carried out. As the duration is not primarily relevant for the assessment of motor function, these endpoints are only considered additionally.

Health status (EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The assessment is not based on the responder analysis presented (response

criterion 15% of the scale range) for the evaluation period up to week 52, but on the mean difference of the change at week 52. There is no statistically significant difference between the treatment arms.

Quality of life

Endpoints on health-related quality of life were not assessed in the PROPEL study.

Side effects

For the endpoints severe adverse events and discontinuation due to adverse events, there was no statistically significant difference between the treatment groups. In the study, infusion-related reactions were also collected using a predefined set of symptoms that occurred between 2 and 96 hours after the infusion. It can be assumed that the infusion-related reactions were also included in the evaluations of the adverse events, so that they were not considered separately. It should also be noted that there was no statistically significant difference between the treatment arms.

Overall assessment

For cipaglucosidase alfa in combination with miglustat as a long-term enzyme replacement therapy for use in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency), based on the PROPEL study, results are available for the endpoint categories of mortality, morbidity and side effects, each in comparison with the appropriate comparator therapy alglucosidase alfa.

There were no deaths in the studies.

The morbidity category includes patient-relevant endpoints on physical functioning (using the R-PAct and PROMIS questionnaires), fatigue, dyspnoea, function of the upper extremities (PROMIS), changes in general physical well-being, breathing effort, muscle power, muscle function, ability to move, activities of daily living, energy levels and muscle pain (using the SGIC), physical resilience (using the 6-minute walk test), motor function (GSGC test) and health status (EQ-5D VAS). There were statistically significant differences in favour of cipaglucosidase alfa in the endpoints of energy level and ability to move as measured by SGIC.

Data on quality of life were not collected in the PROPEL study.

For the side effects, there were no statistically significant differences between the comparator arms in terms of the overall rates of serious adverse events.

In the overall analysis, statistically significant advantages of cipaglucosidase alfa in combination with miglustat over alglucosidase alfa in the category of morbidity (energy level and ability to move, both using SGIC) were shown.

The additional benefit is determined on the basis of these endpoints assessed using SGIC, but the results on the other endpoints of physical and motor function must also be considered in the overall assessment. In this case, there are no data with opposing direction of effect that would call the observed advantages into question, especially for the endpoints collected using the more complex R-PAct and PROMIS instruments.

Since the statistically significant advantages in the endpoints of energy level and ability to move are confirmed, but not in the morbidity endpoints, which were also collected, and in particular not in the endpoints on physical and motor function, the extent of the additional benefit is to be considered minor at best.

Overall, a minor additional benefit was therefore identified for the active ingredient cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa in the treatment of adults with Pompe disease.

Reliability of data (probability of additional benefit)

The pharmaceutical company's approach for transforming the raw values of the data collected using PROMIS means that patients with missing values in individual or several items are not included in the evaluation with a value generated in the scoring. For these patients, the missing total score was replaced by non-response imputation. This results in a high percentage of substituted values in the endpoints of physical functioning (PROMIS Physical Function) and upper extremity function (PROMIS Upper Extremity) (17.6% and 32.9% in the cipaglucosidase alfa arm and 18.4% and 23.7% in the comparator arm). The risk of bias of the results for these endpoints is therefore rated as high.

In the data collected using R-PAct, there are also high percentages of missing values that were replaced by imputation (27.1% in the cipaglucosidase alfa arm and 15.8% in the comparator arm). There is therefore also a high risk of bias for this endpoint.

At study level and for all other endpoints, a low risk of bias is assumed on the basis of the double-blind, randomised study design.

The additional benefit identified is based in particular on the endpoints of energy level and ability to move, which were determined using SGIC. However, as described above, it is relevant in the present assessment that no opposite effects occurred in the other morbidity endpoints. Since the reliability of data for the endpoints on physical functioning and function of the upper extremities is subject to uncertainty due to the high risk of bias in each case, the certainty of the additional benefit is categorised as a hint overall.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Pombiliti with the active ingredient cipaglucosidase alfa. Cipaglucosidase alfa is approved for long-term enzyme replacement therapy for use in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

The G-BA determined alglucosidase alfa as the appropriate comparator therapy.

The double-blind, randomised, placebo-controlled phase III PROPEL study comparing cipaglucosidase alfa in combination with miglustat with alglucosidase alfa was presented for the assessment of additional benefit.

There were no deaths in the study. In the morbidity category, there were statistically significant advantages of cipaglucosidase alfa over the appropriate comparator therapy for

the endpoints of ability to move and energy level in the symptomatology endpoint assessed using the Subject's Global Impression of Change (SGIC). There were no relevant advantages of cipaglucosidase alfa for the other endpoints of physical functioning, fatigue, dyspnoea, function of the upper extremities, physical resilience, motor function and health status.

No data were collected in the category of health-related quality of life. In the side effects category, there were no statistically significant differences between the two treatment arms neither for serious adverse events nor discontinuations due to adverse events.

Overall, there is an additional benefit based on the results of the ability to move and the energy level. Since the positive results are not confirmed in the majority of the morbidity endpoints collected likewise, the extent of the additional benefit is considered to be minor. Due to the high risk of bias of relevant endpoints collected using the PROMIS and R-PAct questionnaires, the reliability of data is categorised as a hint.

In the overall assessment, a hint for a minor additional benefit of cipaglucosidase alfa compared to the appropriate comparator therapy is identified.

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

The information on the number of patients (approx. 170 – 1,760) is based on the target population in statutory health insurance (SHI). The resolution is based on the information from the dossier assessment of the IQWiG (A23-79).

Uncertainties exist for both the lower and upper limits, which are due in particular to the unclear data basis with regard to the information used by the pharmaceutical company for the prevalence. In addition, the pharmaceutical company’s estimate of 5% of LOPD patients suffering from Pompe disease is subject to 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 Pombiliti (active ingredient: cipaglucosidase alfa) at the following publicly accessible link (last access: 12 December 2023):

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

Treatment with cipaglucosidase alfa should only be initiated and monitored by doctors experienced in treating patients with Pompe disease or other congenital metabolic diseases or neruomuscular diseases.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2024).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) 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.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.7 kg).[2]

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 varies from patient to patient 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				
Cipaglucosidase alfa	Continuously, 1 x every 14 days	26.1	1	26.1
Miglustat	Continuously, 1 x every 14 days	26.1	1	26.1
Appropriate comparator therapy				
Alglucosidase alfa	Continuously, 1 x every 14 days	26.1	1	26.1

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes), www.gbe-bund.de

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
Medicinal product to be assessed					
Cipaglucosidase alfa	1,554 mg = 20 mg/-77.7 kg	1 x 1554 mg	15 x 105 mg	26.1	391.5 x 105 mg
Miglustat	260 mg	1 x 260 mg	4 x 65 mg	26.1	104.4 x 65 mg
Appropriate comparator therapy					
Alglucosidase alfa	1,554 mg = 20 mg/ 77.7 kg	1 x 1554 mg	32 x 50 mg	26.1	835.2 x 50 mg

Costs:

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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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					
Cipaglucosidase alfa 105 mg	25 CIS	€ 42,322.24	€ 2.00	€ 2413.74	€ 39,906.50
Miglustat 65 mg	24 HC	€ 1,411.67	€ 2.00	€ 77.53	€ 1,332.14
Appropriate comparator therapy					
Alglucosidase alfa 50 mg	25 CIS	€ 19,569.17	€ 2.00	€ 1,117.00	€ 18,450.17
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 January 2024

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy 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.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

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 Cipaglucosidase alfa

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the

pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for cipaglucosidase alfa (Pombiliti); Pombiliti 105 mg powder for a concentrate for the preparation of an infusion solution; last revised: March 2023

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

At its session on 13 April 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 August 2023, the pharmaceutical company submitted a dossier for the benefit assessment of cipaglucosidase alfa to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 August 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient cipaglucosidase alfa.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 October 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2023. The deadline for submitting statements was 22 November 2023.

The oral hearing was held on 11 December 2023.

By letter dated 12 December 2023, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 12 January 2024.

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 23 January 2024, and the proposed resolution was approved.

At its session on 1 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	13 April 2023	Determination of the appropriate comparator therapy
Working group Section 35a	6 December 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 December 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 December 2023; 16 January 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	23 January 2024	Concluding discussion of the draft resolution
Plenum	1 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 February 2024

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

Prof. Hecken