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
Lonafarnib (Hutchinson-Gilford progeria syndrome or progeroid laminopathy, 12 months and older)

of 6 April 2023

Contents

1. Legal basis

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

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

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

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

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of

the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online 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 lonafarnib on 15 October 2022 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 30 September 2022.

Lonafarnib for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

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

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 16 January 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G22-35) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4

VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of lonafarnib.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of lonafarnib (Zokinvy) in accordance with the product information

Treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation.

Therapeutic indication of the resolution (resolution of 6 April 2023):

- see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

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

Justification:

07-01/0007 study (ProLon1)

ProLon1 is an open-label, single-arm, single-centre phase II study in which 28 patients with Hutchinson-Gilford progeria syndrome or progeroid laminopathy received lonafarnib for up to 30 months. The primary endpoint was an increase in annual weight gain of at least 50% compared to the rate documented at the start of the study. Following ProLon1, the study participants were able to switch to the 09-06-0298 study (triple therapy with lonafarnib, pravastatin and zoledronate).

The study was conducted between May 2007 and November 2009 at Boston Children's Hospital, USA.

09-06/0298 study (ProLon2)

ProLon2 is an open-label, single-centre phase II study without a control arm. In the study, a group of patients with Hutchinson-Gilford progeria syndrome or progeroid laminopathy were treated with a combination therapy of lonafarnib, pravastatin and zoledronate. In the 2nd

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

group, 35 patients were treated with lonafarnib as monotherapy. Since the triple therapy of group 1 does not comply with the product information, only group 2 is considered for the present benefit assessment. ProLon2 consists of a one-week baseline phase and a treatment phase with lonafarnib of 24 months, which can be extended by 12 months, for a maximum treatment duration of 36 months. In the follow-up phase, the test subjects are further observed for 30 days. The primary endpoint was an increase in annual weight gain of at least 50% compared to the rate documented at the start of the study. Following ProLon2, the study participants were able to switch to the 00017050 study, which initially involved treatment with lonafarnib and everolimus.

The study is ongoing and has been conducted at Boston Children's Hospital, USA since March 2009.

Indirect comparison

In addition to the ProLon1 and ProLon2 intervention studies, the pharmaceutical company is submitting a further study with a data cut-off of 1 June 2019, in which patients with HGPS treated with lonafarnib are compared with untreated controls in terms of survival based on data from the "International Progeria Registry" of the Progeria Research Foundation (PRF). This is an indirect comparison without a bridge comparator and methods and evaluations specified post hoc.

To be included in the natural control cohort, patients had to be identified in the International Progeria Registry and not have been previously treated with lonafarnib. The "International Progeria Registry" is fed by data from the PRF's internal patient database and the PRF's international registry, for which patients were identified from case studies, data from the Sunshine Foundation and via web and PubMed searches. According to the study report, the cohorts of treated and untreated subjects with natural history represent the entire global population of patients with HGPS identified to date.
Inclusion criteria for the natural control cohort were a clinical and/or genetic HGPS diagnosis and a known date of birth and death or, in the absence, age at death or known survival status as of 01.01.2018.
A total of 258 subjects with HGPS were identified. Of these, 62 were treated with lonafarnib in the ProLon1 and ProLon2 studies and a further 18 received the triple therapy from the 09-06-0198 study and were not considered for the control population. Furthermore, 2 subjects who were too ill to travel to Boston and 3 more subjects who died before the age of onset of treatment of the youngest treated person from the intervention studies were excluded, leaving a pool of 173 untreated subjects for possible matching. From the pool of 173 untreated persons, a temporally parallel cohort (contemporary population) was formed, consisting of 81 subjects born after 1991 (earliest date of birth of a treated subject from the ProLon1 and ProLon2 studies).
Data are available for 2 follow-up periods. Follow-up is available up to 3 years after start of treatment, censoring subjects after 3 years or at the time of initiation of subsequent therapy in the intervention group (everolimus + lonafarnib or lonafarnib + pravastatin + zoledronate). A second follow-up is available at the time of the "last contact", whereby data from the subsequent therapies are also included.

For the evaluations, a matching procedure was used in which each treated subject from the ProLon1 and ProLon2 studies was assigned an untreated subject for comparison. Sex and continent of residence were the matching variables to check for any confounding.
In the primary matching method (Random Untreated Matching), the treated subjects were sorted in a first step according to their age at the start of treatment. In descending order of age, each treated subject was matched with all untreated subjects who matched the sex and continent of the treated subject and who were still alive at the corresponding age of the start of treatment of the treated subject, as a control pool. From this control pool, one untreated subject was randomly selected as a matching partner, who was then no longer available as a potential matching partner for the remaining treated subjects.
Several other matching procedures were carried out as sensitivity analyses.

Uncertainties of the indirect comparison

Given the extreme rarity of the disease, it is assumed that the selected "International Progeria Registry" represents the best possible or only pool of control subjects for the indirect comparison presented.

When comparing two cohorts without a bridge comparator, knowledge and consideration of all relevant confounders and effect modifiers is necessary to achieve the best possible structural equality. However, the pharmaceutical company does not present the results of a systematic search and assessment of any confounders. The selection of "sex" and "continent" as matching variables are largely based on data availability. According to the EMA, a literature search did not identify any confounders in the therapeutic indication of HGPS. However, especially considering the large variance in the age at which deaths can occur in people with HGPS (2.6- 27.4 years based on data from the Progeria Registry), it remains unclear whether there are other previously unknown prognostic factors that were not collected in the studies or for the control subjects. In addition, in the evaluations including the contemporary cohort, complete matching could only be achieved for the "sex" criterion.
In addition, there is no information on cardiovascular events in the history, or on concomitant medications and supportive therapies in the patients in the control group. Due to the lack of data, it remains unclear whether there are relevant differences between the treatment groups in terms of disease characteristics or disease severity. Any differences in supportive or symptom-based therapy (for example, the use of statins or the treatment of strokes) cannot be ruled out either, nor can their potential impact on patient mortality.
The clinical expert stated in the written opinion that none of the co-therapies used had a proven effect on survival time. However, particularly given the wide variance in the age at which deaths can occur in people with HGPS, the lack of data on supportive or symptom-based therapies, as well as cardiovascular events, adds to uncertainty.

Furthermore, the post-hoc planning and implementation of the evaluations represent a further limitation, and the results sometimes lack important information required for a final assessment, such as censoring reasons or observation periods. The evaluation on the "last contact" also includes information generated during double and triple therapy and the number of censors is lower. However, the results also include any therapeutic effects of these subsequent therapies.

A selection bias cannot be ruled out in this case either, as the exact reasons why certain patients from the "International Progeria Registry" were enrolled in the ProLon 1 and ProLon2 intervention studies and others remained in the untreated, contemporary comparison cohort remain unclear, even when taking into account the inclusion and exclusion criteria of the intervention studies.

In the indirect comparison presented without a bridge comparator, there is a statistically significant difference for overall mortality for the 3-year follow-up period and follow-up to last contact at the data cut-off of 1 June 2019 (hazard ratio [95% CI], p value: 0.17 [0.06; 0.48], 0.0008 and 0.23 [0.12; 0.45], < 0.0001, respectively) to the advantage of lonafarnib over the contemporaneous untreated cohort.

Following the oral hearing, the pharmaceutical company submitted updated data of the cohort study with a data cut-off of 1 August 2021, which were taken into account in the marketing authorisation procedure by the EMA. Compared to the data cut-off of 1 June 2019, there was a revision to the censoring rule so that if a treated subject was censored, the untreated matching partner was also censored and the follow-up time is comparable.

In the updated evaluation, more deaths in the treated group and fewer deaths from the control population are included in the analyses. For overall mortality, there continues to be a statistically significant difference for the 3-year follow-up period and the follow-up to the last contact (hazard ratio [95% CI], p value: 0.28 [0.11; 0.76], 0.0117 and 0.28 [0.15; 0.52], < 0.0001, respectively) to the advantage of lonafarnib over the contemporaneous untreated cohort.

However, the described fundamental uncertainties of the indirect comparison remain.

In summary, due to the large uncertainties of the presented indirect comparison without bridge comparator, it cannot be concluded with sufficient certainty that the effects shown with regard to mortality are not exclusively due to bias. In this context, for example, the evaluation of the entire control population, including subjects born before 1991, shows no statistically significant difference between the treatment groups.

The results of the submitted indirect comparison without a bridge comparator are not considered in the benefit assessment due to the large uncertainties mentioned above.

Mortality

The number of deaths was collected in the ProLon1 and ProLon2 studies as part of the safety assessment.

In the ProLon1 study, one death occurred in a child with classic HGPS at the age of 9 years, and in the still ongoing ProLon2 study, 4 deaths occurred as of the evaluation date of 04.02.2020.

An interpretation and assessment of the data on mortality is not possible due to the missing control group.

Therefore, no statements on the extent of additional benefit can be derived for the mortality category.

Morbidity

Anthropometric parameters

Rate of weight gain, change in BMI and change in body height

Short stature and severe failure to thrive in combination with reduced weight compared to the general population are essential disease characteristics of progeria. Anthropometric measures, or deviations from them, are therefore considered patient-relevant parameters in the present therapeutic indication. Data adjusted for age and sex are preferred to absolute values.

The primary endpoint of the ProLon1 and ProLon2 studies was operationalised as the attainment of at least a 50% increase in the annual rate of weight gain compared to the time of enrolment in the study. Since only absolute values (no standard values) are presented in the available evaluations of the pharmaceutical company, the endpoint cannot be used for the benefit assessment due to the lack of a valid comparison. As this is the primary endpoint of both studies, the "increase in the annual rate of weight gain by at least 50%" is presented additionally in the resolution.

For the endpoints "change in BMI" and "change in body height", only absolute values were presented as opposed to normative values (e.g. Z values) for the changes compared to baseline. As a valid comparison is missing, the endpoint cannot be considered for the benefit assessment either.

Therefore, no statements on the extent of additional benefit can be derived for the morbidity category.

Quality of life

No results on quality of life were presented.

Side effects

The median treatment duration was 809 days in the ProLon1 study and was only slightly shorter at 755 days in the ProLon2 study. No information is available on the observation duration. AEs occurred in all subjects in the course of the studies. Severe AEs of CTCAE grade ≥ 3 were common in both studies. Serious adverse events affected 43% in the ProLon1 study and 34% in the ProLon2 study, with "cerebral ischaemia" (7%) in the ProLon1 study and "myocardial infarction" (11%) in the ProLon2 study being the most common preferred terms.

It can be assumed that a relevant percentage of AEs is due to the symptomatology of the underlying disease. Evaluations in which aspects of the underlying disease are excluded from the AEs are not available. In addition, it is unclear, especially for the ProLon2 study, whether a complete recording of all AEs was possible due to the relatively long intervals between telephone contacts.

The events specified by the pharmaceutical company as AEs of special interest are not taken into account, as they were defined post hoc and moreover not at the request of the regulatory authority.

Against the background of a lack of valid comparison, the small sample size and the limitations in the assessment and evaluation of safety data with regard to the recording of disease symptomatology, no statements on the extent of additional benefit can be derived for the side effects category.

Overall assessment/ conclusion

For lonafarnib for the treatment of patients 12 months of age and older with Hutchinson-Gilford progeria syndrome (HGPS) or progeroid laminopathy, results of the open-label, single-arm phase II ProLon1 and ProLon2 intervention studies are available for the endpoint categories of mortality, morbidity and side effects.
In addition, the pharmaceutical company is presenting a further study in which patients with HGPS treated with lonafarnib are compared with untreated controls with regard to survival on the basis of data from the "International Progeria Registry" of the Progeria Research Foundation. This is a non-adjusted indirect comparison without a bridge comparator. The indirect comparison presented could not be used due to the described limitations.

For the mortality category, no statements on the extent of additional benefit can be derived due to the lack of a control group.

In the morbidity category , no statements on the extent of additional benefit can be derived for the endpoints "rate of weight gain", "change in BMI" and "change in body height" either, as only absolute values were presented for the changes compared to baseline, in contrast to normative values (e.g. z-values), and a valid comparison is missing.

No results were presented in the quality of life category.

Against the background of a lack of valid comparison, the small sample size and the limitations in the assessment and evaluation of safety data with regard to the recording of disease symptomatology, no statements on the extent of additional benefit can be derived for the side effects category.

Quantification of the extent of the additional benefit is not possible on the basis of the data presented. Overall, a non-quantifiable additional benefit is derived for lonafarnib because the scientific data does not allow quantification.

Significance of the evidence

The risk of bias of the ProLon1 and ProLon2 studies is assessed as high due to the uncontrolled study design at study and endpoint level.

Overall, therefore, only a hint for an additional benefit can be derived.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Zokinvy" with the active ingredient lonafarnib. Zokinvy was approved as an orphan drug under "exceptional circumstances" for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a

processing-deficient progeroid laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation.
For the present therapeutic indication, results of the open-label, single-arm phase II ProLon1 and ProLon2 intervention studies are available for the endpoint categories of mortality, morbidity and side effects. In addition, the pharmaceutical company is presenting a further study in which patients with HGPS treated with lonafarnib are compared with untreated controls with regard to survival on the basis of data from the "International Progeria Registry" of the Progeria Research Foundation. This is a non-adjusted indirect comparison without a bridge comparator. The indirect comparison presented could not be used due to the described limitations.

For the mortality category, no statements on the extent of additional benefit can be derived due to the lack of a control group.

In the morbidity category , no statements on the extent of additional benefit can be derived for the endpoints "rate of weight gain", "change in BMI" and "change in body height" either, as only absolute values were presented for the changes compared to baseline, in contrast to normative values (e.g. z-values), and a valid comparison is missing. No results were presented in the quality of life category. Against the background of a lack of valid comparison, the small sample size and the limitations in the assessment and evaluation of safety data with regard to the recording of disease symptomatology, no statements on the extent of additional benefit can be derived for the side effects category. In the absence of robust data for a comparative assessment, it is not possible to quantify the magnitude of the additional benefit based on the data presented.

The risk of bias of the ProLon1 and ProLon2 studies is assessed as high due to the uncontrolled study design at study and endpoint level.

Overall, a hint for a non-quantifiable additional benefit is derived for lonafarnib because the scientific data 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 takes into account the patient numbers stated in the pharmaceutical company’s dossier.

The calculation of the pharmaceutical company is comprehensible and largely plausible. Uncertainties exist, among other things, due to missing information on the epidemiological data quality of the calculation basis (information from the Progeria Research Foundation). In addition, there is no limitation to the age of the patients and no precise limitation of the progeroid laminopathy with one of the corresponding mutations. It remains unclear whether these limitations could have an impact on the calculated number of patients in the SHI target population.

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 Zokinvy (active ingredient: lonafarnib) at the following publicly accessible link (last access: 26 January 2023):

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

Treatment with lonafarnib should only be initiated and monitored by doctors experienced in treating patients with confirmed progeria syndromes or patients with rare genetic metabolic syndromes.

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 01 February 2023).

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.

For dosages depending on body surface area, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied. Children aged 12 months weigh an average of 9.69 kg with an average body height of 0.76 m^2. For adults, the average body weight is 77.0 kg and the average body height is 1.72 m.[3] This results in a body surface area of 0.44 m^2 for children aged 12 months and 1.9 m^2 for adults. The product information of the medicinal product to be assessed only provides specific information up to a body surface area of 1 m^2 on how hard capsules of different potency are to be taken to achieve the target dosage (number of capsules per morning and evening dose). For this reason, a body surface area of 1 m^2 is taken into account as an upper limit within the framework of the cost representation.

2Robert Koch Institute. Contributions to Federal Health Reporting: Reference percentiles for anthropometric measures and blood pressure from the Study on the Health of Children and Adolescents in Germany (KiGGS) [online]. [Accessed: 23.09.2021]. URL: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsB/KiGGS_Referenzperzentile.pdf?__blob=publicationFile

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Lonafarnib	Continuously, 2 x daily	365	1	365.0

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					
Lonafarnib	Patients with a BSA of 0.44 m²				
	150 mg/m² = 66 mg	2 x 150 mg/m² = 1 x 75 mg + 1 x 50 mg	1 x 75 mg + 1 x 50 mg	365.0	365.0 x 75 mg + 365.0 x 50 mg
	Patients with a BSA of 1 m²				
	150 mg/m² = 150 mg	2 x 150 mg/m² = 2 x 150 mg	4 x 75 mg	365.0	1,460 x 75 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.

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					
Lonafarnib 50 mg	30 HC	€ 28,573.53	€ 2.00	€ 2,791.80	€ 25,779.73
Lonafarnib 75 mg	30 HC	€ 42,831.48	€ 2.00	€ 4,187.70	€ 38,641.78
Abbreviations: HC = hard capsules					

LAUER-TAXE® last revised: 1 March 2023

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.

No additionally required SHI services are taken into account for the cost representation.

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 Lonafarnib

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.

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

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

3. Bureaucratic costs calculation

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

4. Process sequence

On 30 September 2022, the pharmaceutical company submitted a dossier for the benefit assessment of lonafarnib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 16 January 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 6 February 2023.

The oral hearing was held on 20 February 2023.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 10 March 2023.

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 28 March 2023, and the proposed resolution was approved.

At its session on 6 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 January 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	15 February 2023	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	20 February 2023	Conduct of the oral hearing
Working group Section 35a	2 March 2023 15 March 2023 22 March 2023	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	28 March 2023	Concluding discussion of the draft resolution
Plenum	6 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 April 2023

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

Prof. Hecken