

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

Resolution of: 6 April 2023 valid until: unlimited  
Entry into force on: 6 April 2023  
Federal Gazette, BAnz AT 22 05 2023 B3

**Therapeutic indication (according to the marketing authorisation of 18 July 2022):**

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 therapeutic indication according to marketing authorisation.

**1. Extent of the additional benefit and significance of the evidence**

Lonafarnib is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with 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.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

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

**Extent of the additional benefit and significance of the evidence of lonafarnib:**

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

## Study results according to endpoints:<sup>1</sup>

### Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	∅	No data available.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available n.a.: not assessable		

### ProLon1 and ProLon2: Non-controlled phase 2 studies

Relevant sub-population: For the present benefit assessment, only patients in the two studies who were treated with lonafarnib as monotherapy in accordance with the marketing authorisation were considered.

### Mortality

Endpoint	Lonafarnib	
	N <sup>a)</sup>	Patients with event n (%)
Deaths		
ProLon1	29	1 (3.4)
ProLon2	35	4 (11.4)
<sup>a)</sup> Corresponds to the number of subjects enrolled. Abbreviations: N = number of patients evaluated; n = number of patients with (at least one) event		

<sup>1</sup> Data from the dossier assessment of the G-BA (published on 16. January 2023), unless otherwise indicated.

## Morbidity

Endpoint	Lonafarnib	
	N	Median (min; max)
Rate of weight gain ( <i>presented additionally</i> )		
<i>Annual rate before start of treatment (kg)<sup>a) b)</sup></i>		
ProLon1	28 <sup>c)</sup>	0.49 (-0.55; 1.69)
ProLon2	22 <sup>c)</sup>	0.58 (-0.44; 2.21)
<i>Annual rate at the end of treatment (kg)<sup>d)</sup></i>		
ProLon1	28 <sup>c)</sup>	0.42 (-0.78; 1.47)
ProLon2	22 <sup>c)</sup>	0.40 (-0.07; 0.72)
	N	Patients with event n (%)
<i>≥ 50% increase in the annual rate</i>		
ProLon1	28 <sup>c)</sup>	11 (39)
ProLon2	22 <sup>c)</sup>	8 (23)
<p>a) ProLon1 study: Calculated from data collected within the year prior to the start of the study and estimated using the slope of a patient-individual least squares regression. The baseline rate of weight gain (kg/month) was recorded and converted to the year by multiplying by 12.</p> <p>b) ProLon2 study: Calculated on the basis of the weights available in the previous year at an interval of at least one month for subjects who were old enough to no longer be on a clear growth curve (3 years or older). Younger subjects and those without sufficient weight history were excluded from the analysis. If the data proved to be non-linear, the rate was estimated from the slope of the secant line (connection of first and last data point).</p> <p>c) Data on the start and end of treatment were available from 28 subjects (100%) in the ProLon1 study and from 22 subjects (63%) in the ProLon2 study.</p> <p>d) Estimated from the slope of the patient-individual least squares regression. If the data proved to be non-linear, the rate was estimated from the slope of the secant line (connection of first and last data point).</p>		
Abbreviations: N = number of patients evaluated; n = number of patients with (at least one) event		

## Health-related quality of life

Health-related quality of life was not collected.

## Side effects

Endpoint	Lonafarnib	
	N <sup>b)</sup>	Patients with event n (%)
<b>Adverse events (AEs)</b>		
ProLon1	28	28 (100)
ProLon2	35	34 (97)

Endpoint	Lonafarnib	
	N <sup>b)</sup>	Patients with event n (%)
<b>Serious adverse events (SAE)</b>		
ProLon1	28	12 (43)
ProLon2	35	12 (34)
<b>Severe adverse events (CTCAE grade 3 or 4)</b>		
ProLon1	28	16 (57)
ProLon2	35	13 (37)
<b>Therapy discontinuation due to adverse events</b>		
ProLon1	28	0
ProLon2	35	0
<b>SAEs with an incidence ≥ 5%, MedDRA system organ class, preferred term</b>		
<b>Infections and infestations, pneumonia</b>		
ProLon1	28	-
ProLon2	35	2 (6)
<b>Cardiac disorders, myocardial infarction</b>		
ProLon1	28	-
ProLon2	35	3 (9)
<b>Nervous system disorders, cerebral ischaemia</b>		
ProLon1	28	2 (7)
ProLon2	35	2 (6)
<p><sup>b)</sup> Corresponds to all subjects with at least 1 dose of lonafarnib</p> <p>Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; (S)AE: (Serious) Adverse Event.</p>		

## 2. Number of patients or demarcation of patient groups eligible for treatment

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

Approx. 5 to 6 patients

### 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](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.

### 4. Treatment costs

#### Annual treatment costs:

Patients 12 months of age and older with 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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lonafarnib	€ 783,795.04 - € 1,880,566.63

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 March 2023)

Costs for additionally required SHI services: not applicable

### 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

Medicinal products with the new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with lonafarnib for the treatment of Hutchinson-Gilford progeria syndrome or progeroid laminopathy on the basis of the marketing authorisation granted under Medicinal Products Act:

- No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.