Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Lorlatinib (new therapeutic indication: non-small cell lung cancer, ALK+, first-line)

of 1 September 2022

At its session on 1 September 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Lorlatinib in accordance with the resolution of 22 November 2019:**

Lorlatinib

Resolution of: 1 September 2022
Entry into force on: 1 September 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 27 January 2022):

Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Therapeutic indication of the resolution (resolution of 1 September 2022):

See new therapeutic indication according to marketing authorisation.

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

Adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor

Appropriate comparator therapy:

– Alectinib

or

– Brigatinib

Extent and probability of the additional benefit of lorlatinib compared to brigatinib:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-31) unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

Indirect comparison: Lorlatinib (CROWN study) vs brigatinib (ALTA-1L study) via the bridge comparator crizotinib

Mortality

Endpoint	Lorlatinib or brigatinib		Crizotinib		Group difference
	N	Median survival time to event [95% CI] *Patients with event n (%)*	N	Median survival time to event [95% CI] *Patients with event n (%)*	HR [95% CI] p value
Overall survival					
Lorlatinib vs crizotinib					
CROWN	149	n.a. *23 (15.4)*	147	n.a. *28 (19.0)*	0.72 [0.41; 1.25]; 0.240[a]
Brigatinib vs crizotinib					
ALTA-1L (3rd data cut-off of 29.01.2021)	137	n.d.[b] *41 (30.0)*	138	n.d.[b] *51 (37.0)*	0.81 [0.53; 1.22]; 0.305[c]
Indirect comparison via bridge comparator[d]:					
Lorlatinib vs brigatinib					0.89 [0.44; 1.77]; 0.736[e, f]

Morbidity

Symptomatology (EORTC QLQ-C30, EORTC QLQ-LC13)	
	no indirect comparison because of insufficient similarity
Health status (EQ-5D VAS)	
	no data for indirect comparison[g]

Health-related quality of life

	no indirect comparison because of insufficient similarity

Side effects

	no indirect comparison because of insufficient similarity

a. Cox proportional hazards model adjusted and log-rank test stratified by presence of CNS metastases at the start of the study (yes / no) and ancestry (Asian / non-Asian).
b. The available data in module 4A reflect the probability of survival after 3 years, but not the median time to event.
c. Cox proportional hazards model and log-rank test stratified by presence of CNS metastases at the start of the study (yes / no) and prior chemotherapy for treatment of advanced or metastatic disease (yes / no).
d. Indirect comparison according to Bucher
e. IQWiG calculation
f. When considering the 2nd data cut-off (28.06.2019) of the ALTA-1L study, a consistent result is obtained for the indirect comparison: HR: 0.79; 95% CI: [0.38; 1.64].
g. The endpoint was only collected in the CROWN study.

Abbreviations used:
HR = hazard ratio; n.d.: no data available; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not achieved; vs = versus

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

approx. 390 - 1,310 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 Lorviqua (active ingredient: lorlatinib) at the following publicly accessible link (last access: 6 May 2022):

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

Treatment with lorlatinib may only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with advanced lung cancer, specialists in internal medicine and pulmonology as well as specialists in pulmonary medicine and doctors from other specialist groups participating in the Oncology Agreement.

ALK evidence

Evidence of ALK-positive NSCLC is required for patient selection for treatment with lorlatinib, as a proven benefit is identified only for these patients. Testing for ALK-positive NSCLC should be carried out by laboratories that have proven expertise in the technology used. Improper test performance can lead to unreliable test results.

This medicinal product was authorised under "conditional authorisation". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lorlatinib	€ 62,076.04
Appropriate comparator therapy:	
Alectinib or brigatinib	
Alectinib	€ 73,482.97
Brigatinib	€ 72,684.67

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2022)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 September 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 1 September 2022

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

Prof. Hecken