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)
Osimertinib (reassessment after the deadline: non-small cell lung cancer, EGFR mutations, adjuvant treatment)

of 19 December 2024

At its session on 19 December 2024, 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. Annex XII is amended as follows:

1. **The information on osimertinib in the version of the resolution of 16 December 2021 (Federal Gazette, BAnz AT 10.02.2022 B7) is repealed.**
2. **Annex XII shall be amended in alphabetical order to include the active ingredient Osimertinib as follows:**

Osimertinib

Resolution of: 19 December 2024
Entry into force on: 19 December 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 21 May 2021):

Tagrisso as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

Therapeutic indication of the resolution (resolution of 19 December 2024):

See therapeutic indication according to marketing authorisation.

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

a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

Appropriate comparator therapy:

Patient-individual therapy with selection of:

- monitoring wait-and-see approach (only for patients in stage IB)

and

- postoperative (adjuvant) systemic chemotherapy with selection of
  - cisplatin in combination with vinorelbine

    and
  - cisplatin in combination with pemetrexed

taking into account the tumour stage and general condition.

Extent and probability of the additional benefit of osimertinib compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

Appropriate comparator therapy:

Monitoring wait-and-see approach

Extent and probability of the additional benefit of osimertinib compared to monitoring wait-and-see approach:

Hint for a major additional benefit.

Study results according to endpoints:[1]

a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

No data available.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A24-72) unless otherwise indicated.

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantages in overall survival.
Morbidity	↑↑	Advantages in the endpoints of recurrence rates and disease-free survival.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↓↓	Disadvantages in the endpoints of severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs, as well as in detail for specific AEs.
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		

ADAURA study

- Comparison: osimertinib **vs** placebo[2]
- Study design: double-blind, randomised, multicentre
- Data cut-offs used:
  - 3rd data cut-off from 27.01.2023 (final analysis of overall survival; used for overall survival)
  - 2nd data cut-off from 11.04.2022 (final DFS analysis; used for morbidity, health-related quality of life and side effects)

[2] The investigations conducted in the placebo arm of the ADAURA study are considered sufficient implementation of the appropriate comparator therapy of the wait-and-see approach.

Mortality

Endpoint	Osimertinib		Placebo		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Mortality (3rd data cut-off from 27.01.2023)					
Overall survival	339	n.r. 42 (12.4)	343	n.r. 82 (23.9)	0.49 [0.34; 0.70]; < 0.001[b]

Morbidity

Recurrences (2nd data cut-off from 11.04.2022)					
Recurrence rate[c]	339	- 94 (27.7)	343	- 211 (61.5)	RR: 0.45 [0.37; 0.54]; < 0.001[d] AD: - 33.8%
Local/ regional	339	- 42 (12.4)	343	- 78 (22.7)	-
Distant recurrence	339	- 45 (13.3)	343	- 107 (31.2)	-
CNS recurrences	339	- 20 (5.9)	343	- 38 (11.1)	-
Local/ regional and distant recurrence	339	- 6 (1.8)	343	- 20 (5.8)	-
Death	339	- 1 (0.3)	343	- 6 (1.7)	-
Disease-free survival[e]	339	65.8 [61.7; n.c.] 94 (27.7)	343	28.1 [22.1; 35.0] 211 (61.5)	0.27 [0.21; 0.34]; < 0.001[b] AD: + 37.7 months

Health-related quality of life

SF-36v2 – Time to 1st deterioration (2nd data cut-off from 11.04.2022)					
Physical Component Summary (PCS) score[f]	339	n.r. 57 (16.8)	343	n.r. 53 (15.5)	0.99 [0.68; 1.44]; 0.944[g]
Mental Component	339	n.r. 98 (28.9)	343	n.r. 89 (25.9)	1.01 [0.76; 1.35];

Summary (MCS) score[h]					0.928[g]

Side effects

Endpoint	Osimertinib		Placebo		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
2nd data cut-off from 11.04.2022					
Total adverse events (presented additionally)					
	337	0.4 [0.3; 0.5] 330 (97.9)	343	1.0 [0.7; 1.0] 309 (90.1)	–
Serious adverse events (SAE)					
	337	n.r. 68 (20.2)	343	n.r. 47 (13.7)	1.28 [0.88; 1.84]; 0.193[g]
Severe adverse events (CTCAE grade 3 or 4)[i]					
	337	n.r. 79 (23.4)	343	n.r. 48 (14.0)	1.55 [1.09; 2.19]; 0.014[g]
Therapy discontinuation due to adverse events					
	337	n.r. 43 (12.8)	343	n.r. 9 (2.6)	3.44 [1.99; 5.93]; < 0.001[g]
Specific adverse events					
Skin and subcutaneous tissue disorders (SOC, AEs)	337	2.7 [1.8; 4.8] 249 (73.9)	343	n.r. 130 (37.9)	2.71 [2.21; 3.33]; < 0.001[g]
ILD and pneumonitis[j] (PTs, SAEs)	337	n.r. 2 (0.6)	343	n.r. 0 (0.0)	n.d.; 0.198[g]
Cardiac events[k] (severe AEs[i])	337	n.r. 4 (1.2)	343	n.r. 1 (0.3)	2.98 [0.51; 17.30]; 0.224[g]
Gastrointestinal disorders (SOC, AEs)	337	1.9 [1.1; 2.5] 243 (72.1)	343	25.0 [19.2; n.c.] 157 (45.8)	2.23 [1.82; 2.72]; < 0.001[g]
included therein:					

Diarrhoea (PT, AEs)	337	n.r. 159 (47.2)	343	n.r. 70 (20.4)	2.64 [2.04; 3.43]; < 0.001[g]
Mouth ulcer (PT, AEs)	337	n.r. 39 (11.6)	343	n.r. 10 (2.9)	3.35 [1.91; 5.87]; < 0.001[g]
Stomatitis (PT, AEs)	337	n.r. 59 (17.5)	343	n.r. 15 (4.4)	3.55 [2.25; 5.60]; < 0.001[g]
Paronychia (PT, AEs)	337	n.r. 92 (27.3)	343	n.r. 5 (1.5)	6.84 [4.59; 10.19]; < 0.001[g]
Loss of appetite (PT, AEs)	337	n.r. 48 (14.2)	343	n.r. 13 (3.8)	3.26 [1.97; 5.39]; < 0.001 [g]
Gastrointestinal disorders (SOC, severe AEs[i])	337	n.r. 21 (6.2)	343	n.r. 3 (0.9)	4.27 [1.91; 9.54]; < 0.001[g]
Investigations (SOC, severe AEs[i])	337	n.r. 14 (4.2)	343	n.r. 4 (1.2)	2.62 [1.03; 6.64]; 0.042[g]

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Effect estimate and 95% CI using U and V statistics from stratified log-rank test; p value via stratified log-rank test; stratification variables: stage (IB vs II vs IIIA), EGFR mutational status (exon 19 deletion vs exon 21 substitution mutation [L858R], either alone or in combination with other EGFR mutations) and descent (Asian vs non-Asian).
[c] Percentage of patients, individual components are shown in the rows below.
[d] Effect estimate, 95% CI and p value using the log-binomial model.
[e] operationalised as the time from the day of randomisation up to 1st occurrence of an event, individual components see recurrence rate
[f] A decrease in [PCS score] by ≥ 9.4 points compared to the start of the study is considered a clinically relevant deterioration (value range of the normalised scale: approx. 7 to approx. 70).
[g] Effect estimate and 95% CI using U and V statistics from unstratified log-rank test; p value via unstratified log-rank test.
[h] A decrease in [MCS score] by ≥ 9.6 points compared to the start of the study is considered a clinically relevant deterioration (value range of the normalised scale: approx. 6 to approx. 70).
[i] Operationalised as CTCAE grade ≥ 3
[j] PT collection of the pharmaceutical company. In the intervention arm, interstitial lung disease occurred in 1 patient and pneumonitis in 1 patient.
[k] Operationalised via the SMQ heart failure and the SMQ cardiomyopathy

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; ILD = interstitial lung disease; n.d.: no data available; CI = confidence interval; MCS = Mental Component Summary score; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PT = preferred term; PCS = Physical Component Summary score; RCT = randomised controlled trial; RR = relative risk; SF-36v2 = Short Form-36 Health Survey Version 2; SMQ = standardized MedDRA query; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus; CNS = central nervous system

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

a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

and

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

Approx. 640 - 930 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 Tagrisso (active ingredient: osimertinib) at the following publicly accessible link (last access: 30 August 2024):

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

Treatment with osimertinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with non-small cell lung carcinoma, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

4. Treatment costs

Annual treatment costs:

a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Osimertinib	€ 66,095.17
Appropriate comparator therapy:	
Patient-individual therapy with selection of:	

Designation of the therapy	Annual treatment costs/ patient
- monitoring wait-and-see approach (only for patients in stage IB)	
Monitoring wait-and-see approach	Not calculable
and	
- postoperative (adjuvant) systemic chemotherapy with selection of	
o Cisplatin in combination with vinorelbine	
Cisplatin	€ 2,274.18
Vinorelbine	€ 5,008.76 - € 6,247.29
Total:	€ 7,282.94 - € 8,521.47
Additionally required SHI services:	€ 271.70 - € 341.48
and	
o cisplatin in combination with pemetrexed	
Cisplatin	€ 2,009.18
Pemetrexed	€ 18,764.86
Total:	€ 20,774.04

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 December 2024)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Appropriate comparator therapy:					
Cisplatin in combination with vinorelbine					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	34.8	€ 3,480
cisplatin in combination with pemetrexed					
Cisplatin	Surcharge for production of a parenteral	€ 100	1	17.4	€ 1,740

	preparation containing cytostatic agents				
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Osimertinib	€ 66,095.17
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Not calculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 December 2024)

Costs for additionally required SHI services: not applicable

5. Designation of 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 the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

a) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) Adults with stage IB-IIIA NSCLC, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for it

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 19 December 2024.

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

Berlin, 19 December 2024

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

Prof. Hecken