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
Asciminib (chronic myeloid leukaemia, Ph+, after ≥ 2 prior therapies)

of 16 March 2023

At its session on 16 March 2023, 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 shall be amended in alphabetical order to include the active ingredient Asciminib as follows:

Asciminib

Resolution of: 16 March 2023
Entry into force on: 16 March 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 25 August 2022):

Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors (see section 5.1).

Therapeutic indication of the resolution (resolution of 16 March 2023):

See therapeutic indication according to marketing authorisation.

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

Asciminib 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).

<u>Adults with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors</u>

Extent of the additional benefit and significance of the evidence of asciminib:

Indication of a minor additional benefit

Study results according to endpoints:[1]

Adults with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors

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	↔	Overall, no relevant difference
Health-related quality of life	∅	No data available
Side effects	↑↑	Advantages in the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to 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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

1 Data from the dossier assessment of the G-BA (published on 2. January 2023), unless otherwise indicated.

ASCEMBL study: Asciminib **vs** bosutinib; controlled, randomised, open-label phase III study; data cut-off of 6.10.2021

Mortality

Endpoint	**Asciminib**		**Bosutinib**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI][b] p value[c] Absolute difference (AD)[a]
Overall survival					
	157	n.r. 5 (3.2)	76	n.r. 2 (2.6)	2.29 [0.27; 19.59] 0.438

Morbidity

Endpoint	**Asciminib**		**Bosutinib**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk (RR) [95% CI][d] p value Absolute difference (AD)[a]
Molecular response (MMR)					
MMR at week 24	157	40 (25.5)	76	10 (13.2)	1.93 [1.03; 3.62] 0.029 AD = + 12.3%
MMR at week 96	157	59 (37.6)	76	12 (15.8)	2.38 [1.36; 4.16] < 0.001 AD = + 21.8%

Endpoint	Asciminib		Bosutinib		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][b] p value[c] Absolute difference (AD)[a]
Progression to the blast phase					
	157	n.r. 3 (1.9)	76	n.r. 4 (5.3)	0.29 [0.06; 1.32] 0.089
	Asciminib		**Bosutinib**		Intervention vs control
	N	MD (95% CI)[g]	N	MD (95% CI)[g]	MD [95% CI][e] p value
MDASI-CML – mean change up to week 8					
Severe disease-related symptoms	157	-0.4 [-0.6; -0.2]	76	0.1 [-0.2; 0.4]	-0.5 [-0.9; -0.1] 0.007 Hedges´g[h] -0.35 [95% CI: -0.64; -0.07]
Extent of impairment of daily life	157	-0.2 [-0.6; 0.1]	76	-0.1 [-0.6; 0.4]	-0.1 [-0.7; 0.5] 0.769
Health status (EQ-5D-VAS – mean change up to week 8)					
	157	1.5 [-1.6; 4.7]	76	-0.6 [-5.3; 4.1]	2.1 [-3.4; 7.6] 0.450
PGI-C – mean change up to week 12					
	157	2.7 [2.5; 2.9]	76	3.0 [2.7; 3.3]	-0.3 [-0.7; 0.0] 0.060

Health-related quality of life

No data available.

Side effects

Endpoint	Asciminib		Bosutinib		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][f] p value[g] Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	156	0.66 [0.26; 0.95] 142 (91)	76	0.66 [0.26; 0.95] 74 (97.4)	-
Serious adverse events (SAEs)					
	156	n.r. 28 (17.9)	76	n.r. 20 (26.3)	0.50 [0.28; 0.90] 0.018
Severe adverse events (CTCAE grade 3 or 4)					
	156	9.26 [3.25; 21.19] 88 (56.4)	76	3.48 [1.84; 8.31] 52 (68.4)	0.68 [0.48; 0.96] 0.028 AD = + 5.78 months
Therapy discontinuation due to adverse events					
	156	n.r. 12 (7.7)	76	n.r. 20 (26.3)	0.21 [0.10; 0.44] < 0.001

Endpoint	Asciminib		Bosutinib		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Hazard ratio [95% CI][f] p value[g] Absolute difference (AD)[a]
Severe AEs with incidence ≥ 5% (SOC, PT)					
Investigations	156	28 (17.9)	76	24 (31.6)	0.45 [0.26; 0.79] 0.004 AD = -13.7%
Alanine amino-transferase increased	156	1 (0.6)	76	11 (14.5)	0.04 [0.01; 0.31] < 0.001 AD = - 13.9%
Aspartate aminotransferase increased	156	3 (1.9)	76	5 (6.6)	0.23 [0.05; 0.95] 0.027 AD = - 4.7%
Lipase increased	156	6 (3.8)	76	4 (5.3)	0.61 [0.17; 2.16] 0.435
Gastrointestinal disorders	156	6 (3.8)	76	12 (15.8)	0.18 [0.06; 0.48] < 0.001 AD = - 12%
Diarrhoea	156	0	76	8 (10.5)	n.a.
Vascular diseases	156	14 (9.0)	76	3 (3.9)	1.67 [0.47; 5.87] 0.421
Hypertension	156	10 (6.4)	76	3 (3.9)	1.27 [0.35; 4.68] 0.718
Blood and lymphatic system disorders	156	36 (23.1)	76	14 (18.4)	1.31 [0.71; 2.43] 0.398
Neutropenia	156	24 (15.4)	76	9 (11.8)	1.31 [0.61; 2.82] 0.492
Thrombocytopenia	156	28 (17.9)	76	5 (6.6)	2.79 [1.08; 7.23] 0.027 AD = + 11.3%

Endpoint	Asciminib		Bosutinib		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Hazard ratio [95% CI][f] p value[g] Absolute difference (AD)[a]
Metabolic and nutrition disorders	156	11 (7.1)	76	4 (5.3)	1.15 [0.36; 3.61] 0.816
Respiratory, thoracic and mediastinal disorders	156	0	76	4 (5.3)	n.a.
Skin and subcutaneous tissue disorders	156	1 (0.6)	76	8 (10.5)	0.06 [0.01; 0.45] < 0.001 AD = - 9.9%
SAE with an incidence ≥ 5% (SOC)					
Skin and subcutaneous tissue disorders	156	0	76	4 (5.3)	n.a.
AEs of special interest (SOC, PT)					
Heart failure (clinical events)					
Grade ≥ 3	156	3 (1.9)	76	1 (1.3)	1.16 [0.12; 11.30] 0.898
SAE	156	3 (1.9)	76	1 (1.3)	1.16 [0.12; 11.30] 0.898
Oedema and fluid retention					
Grade ≥ 3	156	0	76	3 (3.9)	n.a.
SAE	156	0	76	2 (2.6)	n.a.
Gastrointestinal toxicity					
Grade ≥ 3	156	4 (2.6)	76	9 (11.8)	0.18 [0.05; 0.58] 0.001 AD = - 9.2%
SAE	156	2 (1.3)	76	1 (1.3)	0.77 [0.07; 8.70] 0.834

Endpoint	Asciminib		Bosutinib		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Hazard ratio [95% CI][f] p value[g] Absolute difference (AD)[a]
Bleeding					
Grade ≥ 3	156	3 (1.9)	76	1 (1.3)	1.12 [0.11; 11.03] 0.923
SAE	156	2 (1.3)	76	0	n.a.
Hepatotoxicity (including laboratory parameters)					
Grade ≥ 3	156	3 (1.9)	76	13 (17.1)	0.09 [0.03; 0.32] < 0.001 AD = - 15.2%
SAE	156	0	76	0	n.a.
Hepatotoxicity (clinical events)					
Grade ≥ 3	156	0	76	0	n.a.
SAE	156	0	76	0	n.a.
Hypersensitivity					
Grade ≥ 3	156	1 (0.6)	76	7 (9.2)	0.06 [0.01; 0.53] < 0.001 AD = - 8.6%
SAE	156	0	76	4 (5.3)	n.a.
Ischaemia of the heart and central nervous system					
Grade ≥ 3	156	5 (3.2)	76	2 (2.6)	0.90 [0.17; 4.72] 0.904
SAE	156	3 (1.9)	76	1 (1.3)	1.15 [0.12; 11.33] 0.902
Myelosuppression (erythropenia)					
Grade ≥ 3	156	2 (1.3)	76	3 (3.9)	0.30 [0.05; 1.79] 0.161
SAE	156	0	76	0	n.a.

Endpoint	Asciminib		Bosutinib		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Hazard ratio [95% CI][f] p value[g] Absolute difference (AD)[a]
Myelosuppression (neutropenia)					
Grade ≥ 3	156	29 (18.6)	76	11 (14.5)	1.29 [0.64; 2.58] 0.476
SAE	156	0	76	0	n.a.
Mylosuppression (leukopenia)					
Grade ≥ 3	156	29 (18.6)	76	11 (14.5)	1.29 [0.64; 2.58] 0.476
SAE	156	1 (0.6)	76	0	n.a.
Myelosuppression (thrombocytopenia)					
Grade ≥ 3	156	35 (22.4)	76	7 (9.2)	2.58 [1.14; 5.80] 0.018
SAE	156	2 (1.3)	76	0	n.a.
Myelosuppression (cytopenia affecting several blood cell lines)					
Grade ≥ 3	156	0	76	1 (1.3)	n.a.
SAE	156	0	76	1 (1.3)	n.a.
Pancreatic toxicity					
Grade ≥ 3	156	6 (3.8)	76	4 (5.3)	0.61 [0.17; 2.16] 0.435
SAE	156	0	76	0	n.a.
Prolongation of the QTc interval					
Grade ≥ 3	156	4 (2.6)	76	0	n.a.
SAE	156	2 (1.3)	76	0	n.a.
Reproductive toxicity					
Grade ≥ 3	156	2 (1.3)	76	0	n.a.
SAE	156	0	76	0	n.a.

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] Cox regression model (hazard ratio) stratified by presence of MCyR (MCyR vs no MCyR) according to IRT. 95% confidence intervals were calculated using Brookmeyer and Crowley (1982).
[c] two-sided p value from log-rank test, stratified by presence of MCyR (MCyR vs no MCyR) according to

IRT.
[d] Cochran-Mantel-Haenszel stratified by presence of MCyR (MCyR vs no MCyR) according to IRT.
[e] A MMRM with treatment, MCyR according to IRT, baseline value, age, time and time*treatment was used as the
fixed terms.
[f] HR calculated post hoc using Cox proportional hazards model with the covariate treatment, stratified by presence of an MCyR (MCyR vs no MCyR) according to IRT.
[g] Calculation of the two-sided p value post hoc from log-rank test, stratified by presence of an MCyR (MCyR vs no MCyR) according to IRT.
[h] Calculation of the G-BA

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D-VAS = European Quality of Life Questionnaire 5 Dimensions - Visual Analogue Scale; HR = hazard ratio; IRT = Interactive Response Technology; n.d. = no data; CI = confidence interval; MDASI-CML = M.D. Anderson Symptom Inventory - Chronic Myeloid Leukaemia; MedDRA = Medical Dictionary for Regulatory Activities; MCyR = Good Cytogenetic Response; MMRM = Mixed Model for Repeated Measures; MD = Mean Difference; N = Number of patients evaluated; n = Number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PGI-C = Patient Global Impression of Change; PT = preferred terms; RR = relative risk; SD = standard deviation; SOC = system organ class; (S)AE = (serious) adverse event; vs = versus

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

Adults with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors

Approx. 840 to 1,150 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 Scemblix (active ingredient: asciminib) at the following publicly accessible link (last access: 12 December 2022):

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

Treatment with asciminib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with chronic myeloid leukaemia.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Asciminib	€ 88,815.73

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

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with asciminib for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in the chronic phase (Ph+ CML-CP) who have previously been treated with two or more tyrosine kinase inhibitors:

Adults with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors

- 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 March 2023.

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

Berlin, 16 March 2023

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

Prof. Hecken