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: Bosutinib (reassessment after the deadline: chronic myelogenous leukaemia, Ph+, first-line)

of 19 November 2021

At its session on 19 November 2021, 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 on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on bosutinib in the version of the resolution of 22 November 2018 (Federal Gazette, BAnz AT 17.12.2018 B3) is repealed.
2. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of bosutinib, in accordance with the resolution in the version of 21 February 2019, for the therapeutic indication "...is indicated for the treatment of adult patients with Ph+ CML in the chronic phase (CP), accelerated phase (AP) and blast phase (BP), previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options":

Bosutinib

Resolution of: 19 November 2021
Entry into force on: 19 November 2021
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 23 April 2018):

Bosulif is indicated for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).

Therapeutic indication of the resolution (resolution of 19 November 2021):

see therapeutic indication according to marketing authorisation

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

Adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).

Appropriate comparator therapy for bosutinib:

- imatinib

or

- nilotinib

or

- dasatinib

Extent and probability of the additional benefit of bosutinib compared to imatinib:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph^+ CML)

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	↔	No relevant difference for the benefit assessment
Health-related quality of life	↔	No relevant difference for the benefit assessment
Side effects	↓	Disadvantages in the endpoints on discontinuation due to AE and severe AE (CTCAE grade ≥ 3) and in detail, advantages and disadvantages in the 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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

BFORE study: Bosutinib **vs** imatinib
Open-label, randomised controlled trial (data cut-off 12.06.2020)

Relevant sub-population: Sub-population with Philadelphia chromosome (modified ITT population (mITT))

Mortality

Endpoint	Bosutinib		imatinib		Intervention vs Control
	N	Median survival time in weeks [95% CI] *Patients with event n (%)*	N	Median survival time in weeks [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value[b] Absolute difference (AD)[a]
Overall survival					
	246	n.a. 12 (4.9)	241	n.a. 14 (5.8)	0.80 [0.37; 1.73] 0.564

[1] Data from the dossier assessment of the IQWiG (A21-134) and from the addendum (A21-134), unless otherwise indicated.

Morbidity

Endpoint	Bosutinib		imatinib		Intervention vs Control
	N	Median survival time in weeks [95% CI] *Patients with event n (%)*	N	Median survival time in weeks [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value[b] Absolute difference (AD)[a]
Molecular response					
MMR after 12 months[g]	246	36.1 [11.9; 241.9] 182 (74)	241	47.7 [12.1; 216.1] 158 (65.6)	1.32 [1.08; 1.63] 0.0123 AD: +11.6 weeks
Transition to the blast phase					
	246	-[c] 3 (1.2)	241	-[c] 1 (0.4)	2.89 [0.30; 28.03] 0.336
Health status (EQ-5D VAS)					
≥ 7 points	246	221.6 [84.7; n.c.] 110 (44.7)	241	n.a. [108.3; n.c.] 100 (41.5)	1.07 [0.82; 1.41] 0.610
≥ 10 points	246	240.6 [110.3; n.c.] 103 (41.9)	241	n.a. [132.9; n.c.] 94 (39.0)	1.04 [0.78; 1.38] 0.784
≥ 15 points[d]	246	n.a. [241.0; n.c.] 72 (29.3)	241	n.a. 62 (25.7)	1.09 [0.78; 1.54] 0.608

Health-related quality of life

Endpoint	**Bosutinib**		**imatinib**		Intervention vs Control
	N	Median survival time in weeks [95% CI] *Patients with event n (%)*	N	Median survival time in weeks [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value[b] Absolute difference (AD)[a]
FACT-Leu total score[d]	246	n.a. 51 (20.7)	241	n.a. 44 (18.3)	1.16 [0.77; 1.73] 0.477
Physical well-being[d]	246	n.a. [241.0; n.c.] 86 (35.0)	241	n.a. 86 (35.7)	0.92 [0.68; 1.25]
Social well-being[d]	246	n.a. [96.1; n.c.] 103 (41.9)	241	240.9 [144.1; n.c.] 92 (38.2)	1.13 [0.86; 1.50]
Emotional well-being[d]	246	n.a. [192.0; n.c.] 92 (37.4)	241	n.a. 77 (32.0)	1.20 [0.88; 1.62]
Functional well-being[d]	246	n.a. [133.4; n.c.] 98 (39.8)	241	n.a. 73 (30.3)	1.38 [1.02; 1.87]
FACT-LeuS[d]	246	n.a. 48 (19.5)	241	n.a. 52 (21.6)	0.85 [0.57; 1.26]

Side effects

Endpoint	**Bosutinib**		**imatinib**		Intervention vs Control
	N	Median in weeks [95% CI] *Patients with event n (%)*	N	Median in weeks [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value[b] Absolute difference (AD)[a]
Total adverse events[e] (presented additionally)					
	246	0.4 [0.3; 0.7] 243 (98.8)	239	1.1 [0.9; 1.1] 236 (98.7)	-

Endpoint	Bosutinib		imatinib		Intervention vs Control
	N	Median in weeks [95% CI] *Patients with event n (%)*	N	Median in weeks [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value[b] Absolute difference (AD)[a]
Serious adverse events (SAE) [e]					
	246	n.a. [224.1; n.c.] 91 (37.0)	239	n.a. 65 (27.2)	1.37 [1.00; 1.89] 0.051
Severe adverse events (CTCAE grade 3 or 4) [e,f]					
	246	21.1 [12.1; 41.7] 182 (74.0)	239	107.1 [49.9; 168.1] 138 (57.7)	1.55 [1.24; 1.93] < 0.001 AD: -86 weeks
Subgroups by age					
< 65 years	198	24.9 [19.4; 61.1] 139 (70.2)	198	83.3 [41.0; 168.1] 116 (58.6)	1.34 [1.04; 1.71] 0.020 AD: -58.4 weeks
≥ 65 years	48	7.6 [3.7; 12.1] 43 (89.6)	41	163.1 [23.6; n.c.] 23 (56.1)	2.80 [1.67; 4.69] <0.001 AD: -155.5 weeks
				Interaction	0.011
Therapy discontinuations due to adverse events[e]					
	246	n.a. 62 (25.2)	239	n.a. 33 (13.8)	1.82 [1.19; 2.77] 0.005
Specific adverse events					
Eye disorders	246	n.a. 39 (15.9)	239	135.4 [62.1; n.c.] 114 (47.7)	0.25 [0.17; 0.36] < 0.001
Gastrointestinal disorders	246	1.0 [0.6; 1.4] 208 (84.6)	239	9.4 [5.3; 21.3] 162 (67.8)	1.90 [1.54; 2.35] < 0.001 AD: -8.4 weeks

Endpoint	Bosutinib		imatinib		Intervention vs Control
	N	Median in weeks [95% CI] *Patients with event n (%)*	N	Median in weeks [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value[b] Absolute difference (AD)[a]
Oedema, peripheral	246	n.a. 18 (7.3)	239	n.a. 38 (15.9)	0.42 [0.24; 0.73] 0.002
Musculoskeletal and connective tissue disorders	246	n.a. [166.7; n.c.] 98 (39.8)	239	19.1 [8.1; 48.4] 145 (60.7)	0.45 [0.35; 0.59] < 0.001
Pruritus	246	n.a. 27 (11.0)	239	n.a. 9 (3.8)	3.02 [1.42; 6.43] 0.003
Neutropenia	246	n.a. 16 (6.5)	239	n.a. 28 (11.7)	0.54 [0.29; 1.01] 0.049
Thrombocytopenia	246	n.a. 23 (9.3)	239	n.a. 10 (4.2)	2.31 [1.10; 4.86] 0.023
Cardiac disorders	246	n.a. 15 (6.1)	239	n.a. 4 (1.7)	3.66 [1.21; 11.04] 0.014
Diarrhoea	246	n.a. 22 (8.9)	239	n.a. 3 (1.3)	7.35 [2.20; 24.56] < 0.001
Impairment of liver function	246	n.a. 66 (26.8)	239	n.a. 10 (4.2)	7.08 [3.64; 13.77] < 0.001
Lipase increased	246	n.a. 32 (13.0)	239	n.a. 13 (5.4)	2.44 [1.28; 4.65] 0.005

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] for all endpoints except transition to blast phase: Cox proportional hazards model and log-rank test, each stratified by Sokal score and geographic region; for transition to blast phase: proportional sub-distribution hazards model considering the competing risks of therapy discontinuation (except due to progression) and death, stratified by Sokal score and geographic region
[c] the median given by the pharmaceutical company cannot be interpreted meaningfully due to the small number of events
[d] patients with a first-time deterioration of ≥ 15% of the scale range. This corresponds to a deterioration of the following values: EQ-5D VAS: ≥ 15 points, FACT-Leu total score: ≥ 26.4 points, physical well-being (PWB), social well-being (SWB), and functional well-being (FWB): ≥ 4.2 points, emotional well-being (EWB): ≥ 3.6 points, additional leukaemia-specific problems (LeuS): ≥ 10.2 points.
[e] with exclusion of progression-associated AEs (PT: acute myeloid leukaemia, chronic myelogenous leukaemia and leukaemic retinopathy); when considering all AEs, for the endpoints SAEs, severe AEs, and discontinuation due to AEs, the number of patients with (at least 1) event increases by 1 in the control arm, while it remains unchanged in the intervention arm.

[f] operationalised as CTCAE grade ≥ 3
[g] Information from the dossier of the pharmaceutical company

Abbreviations used:
AD = absolute difference; CMQ = Customised MedDRA Queries; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = European Quality of Life 5-Dimensions Questionnaire; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT: Preferred Term; RCT = randomised controlled trial; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

approx. 760 to 890 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 Bosulif (active ingredient: bosutinib) at the following publicly accessible link (last access: 2 September 2021):

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

Initiation and monitoring of treatment with bosutinib should be performed only by specialists in internal medicine, haematology and oncology, experienced in the therapy of patients with chronic myelogenous leukaemia.

4. Treatment costs

Annual treatment costs:

a) Adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Bosutinib	€ 32,757.32
Appropriate comparator therapy:	
dasatinib	€ 12,435.55
imatinib	€ 2,005.92
nilotinib	€ 47,908.82

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 November 2021)

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 19 November 2021.

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

Berlin, 19 November 2021

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

Prof. Hecken