Resolution
by the Federal Joint Committee
on an amendment to the Pharmaceutical Directive (AM-RL):
Appendix XII – Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a
Bosutinib

from 17 October 2013

In its session on 17 October 2013, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 8 October 2013 (Federal Gazette, AT 29.10.2013 B1), as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient bosutinib:

Bosutinib

Therapeutic indication

Bosulif® is indicated for the treatment of adult patients with chronic-phase, accelerated-phase and blast-phase Philadelphia-chromosome-positive chronic myelogenous leukaemia previously treated with one or more tyrosine-kinase inhibitors and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

1. Extent of additional benefit of the pharmaceutical

Bosutinib is authorized as a pharmaceutical for the treatment of a rare disease in accordance with EC regulation number 141/2000 of the European Parliament and Council of 16 December 1999 on orphan drugs. In accordance with the German Social Code, Book Five (SGB V), section 35a, paragraph 1, sentence 10, the additional medical benefit has been proved through market authorization.

In accordance with the rules of procedure of the Federal Joint Committee, chapter 5, section 12, paragraph 1, number 1, sentence 2, the Federal Joint Committee determines the extent of the additional benefit for the number of patients and patient groups for whom a therapeutically significant additional benefit exists. This quantification of the additional benefit has been conducted in accordance with the criteria laid out in the Rules of Procedure, chapter 5, section 5, paragraph 7, numbers 1 to 4.

Extent of additional benefit:

Not quantifiable

Study results according to endpoints[1]:

Bosutinib in the chronic phase (CP)				Bosutinib in advanced CML			
Second-line therapy		Third- and fourth-line therapy		Accelerated phase (AP)		Blast phase (BP)	
Mortality							
Overall survival[2]							
N	Deaths n (%)	N	Deaths n (%)	N	Deaths n (%)	N	Deaths n (%)
15	6 (40.0%)	21	5 (23.8%)	5	3 (60.0%)	11	9 (81.8%)

[1] Data for the study 3160A4-200-WW target population from the G-BA benefit assessment and the pharmaceutical company dossier.

[2] Data cut-off 28 March 2011.

Bosutinib in the chronic phase (CP)				Bosutinib in advanced CML			
Second-line therapy		Third- and fourth-line therapy		Accelerated phase (AP)		Blast phase (BP)	
Morbidity							
N	Incidents n (%)	N	Incidents n (%)	N	Incidents n (%)	N	Incidents n (%)
Cytogenetic response (CyR): major cytogenetic response (MCyR)							
15	5 (33.3%)	21	6 (28.6%)	5	2 (40.0%)	11	2 (18.2%)
– Of those: complete cytogenetic response (CCyR)							
15	4 (26.7%)	21	4 (19.0%)	5	2 (40.0%)	11	2 (18.2%)
Molecular response (MR): major molecular response (MMR)							
15	4 (26.7%)	21	3 (14.3%)	5	1 (20.0%)	11	0
Haematological response (HR): complete haematological response (CHR)[3]							
15	n.a	21	7 (33.3%)	5	n.a	11	n.a
Progression-free survival[4]							
N	Number of patients with progression; median PFS	N	Number of patients with progression; median PFS	N	Number of patients with progression; median PFS	N	Number of patients with progression; median PFS
15	n.a	21	n.a	5	n.a.	11	n.a
Health-related quality of life							
Overall health status (EQ-5D)							
No applicable data are available for the target population.							
Fact-Leu							
No applicable data are available for the target population.							

Bosutinib in the chronic phase (CP)				Bosutinib in advanced CML				Bosutinib (target population, overall)	
Second-line therapy		Third- and fourth-line therapy		Accelerated phase (AP)		Blast phase (BP)			
Side effects									
N	Results n (%)	N	Results n (%)	N	Results n (%)	N	Results n (%)	N	Results n (%)
Overall rate AE									
15	15 (100%)	21	21 (100%)	5	5 (100%)	11	11 (100%)	52	52 (100%)
Overall rate SAE									
15	6 (40.0%)	21	10 (47.6%)	5	4 (80.0%)	11	8 (72.7%)	52	28 (53.8%)
AE CTCAE grades 3 and 4									
15	11 (73.3%)	21	12 (57.1%)	5	5 (100%)	11	8 (72.7%)	52	36 (69.2%)
Termination of treatment due to UE									
15	4 (26.7%)	21	5 (23.8%)	5	1 (20.0%)	11	3 (27.3%)	52	13 (25.0%)
Frequent AE/AE of particular interest									
Disorders of the blood and lymphatic system									
15	6 (40.0%)	21	9 (42.9%)	5	4 (80.0%)	11	6 (54.5%)	52	25 (48.1%)
Disorders of the blood and lymphatic system CTCAE grades 3 and 4									
15	5 (33.3%)	21	5 (23.8%)	5	3 (60.0%)	11	5 (45.5%)	52	18 (34.6%)
Liver and gall bladder disorders: Elevated serum transaminases (ALT + AST)									
15	4 (26.7%)	21	6 (28.6%)	5	0	11	3 (27.3%)	52	13 (25.0%)
Elevated serum transaminases (CTCAE grades 3 and 4)									
15	0	21	3 (14.3%)	5	0	11	0	52	3 (5.8%)

[3] Many patients achieved a response lower than CHR, e.g. MMR or MCyR. These patients are not included in the CHR calculation, as achieving MMR or MCyR usually, but not always, requires achieving CHR.

[4] No information on the target population is available.

Bosutinib in the chronic phase (CP)				Bosutinib in advanced CML				Bosutinib (target population, overall)	
Second-line therapy		Third- and fourth-line therapy		Accelerated phase (AP)		Blast phase (BP)			
Diseases of the gastrointestinal tract									
15	13 (86.7%)	21	21 (100%)	5	5 (100%)	11	9 (81.8%)	52	48 (92.3%)
Diseases of the gastrointestinal tract (CTCAE grades 3 and 4)									
15	1 (6.7%)	21	2 (9.5%)	5	2 (40.0%)	11	5 (45.5%)	52	10 (19.2%)
Cardiac disorders: QTc prolongation CTCAE grades 3 and 4									
15	0	21	0	5	0	11	0	52	0
Immunological disorders: Hypersensitivity									
15	0	21	1 (4.8%)	5	0	11	0	52	1 (1.9%)

Abbreviations used: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = common terminology criteria for adverse events, EQ-5D = questionnaire to measure quality of life, FACT-Leu = leukaemia-specific questionnaire to measure quality of life, HR = hazard ratio, n.a = not available, n = number of patients with events, N = total number of patients with data on relevant endpoint, PFS = progression-free survival, QTc = time interval between start of Q wave and end of T wave, (S)AE = (serious) adverse events

2. Number of patients and criteria for defining patients eligible for treatment

   Target population: approx. 380 to 500 patients

3. Requirements for quality-assured administration

   The specifications outlined in the product information are to be followed. The European Medicines Agency (EMA) addresses myelosuppression as well as hepatic, gastro-intestinal, cardiac, and immunological side effects as adverse events of particular significance in EPAR. Patients must be informed of risks mentioned and carefully monitored for relevant signs.

   The EMA provides the contents of the product information on Bosulif® (active ingredient: bosutinib) at the following public link (last accessed: 10 September 2013):

   http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002373/WC500141721.pdf

   This pharmaceutical was authorized by the EMA under a "conditional approval" scheme. That means that additional proof of benefit is expected for this pharmaceutical. The EMA will assess new information on this pharmaceutical at least once a year, and update the summary of product characteristics if necessary.

   Treatment must be initiated and monitored by an internist for haematology and oncology experienced in the treatment of this disease.

4. Costs of treatment

   Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Number of treatment days per patient per year
Bosutinib	1 x 500 mg daily	ongoing	365	365

   Consumption:

Description of therapy	Strength (mg)[5]	Number/amount per pack	Average annual consumption (coated tablets)
Bosutinib	500	28	365

   Costs:

   Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)	Cost after legally mandated rebates
Bosutinib	€6,166.21	€5,366.92 [€1.85[6]; €797.44[7]]

   "Lauer-Taxe", effective: 1 September 2013

[5] In accordance with the recommended dosage, the strength shown is 500 mg (500 mg once daily).

[6] Rebate in accordance with SGB V, section 130.

[7] Rebate in accordance with SGB V, section 130a.

Costs for additional, necessary statutory health insurance (SHI) benefits:

None

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Bosutinib	€69,961.64

II.

Validity

1. This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 17 October 2013.
2. This resolution remains valid until 15 October 2018.

The justification for this resolution will be published on the website of the Federal Joint Committee at www.g-ba.de.

Berlin, 17 October 2013

The Federal Joint Committee in
accordance with SGB V, section 91

The Chair
Hecken