Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V – Ponatinib

of 23 January 2014

At its session on 23 January 2014, the Federal Joint Committee resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 28 January 2015 (Federal Gazette, BAnz AT 14 February 2014 B2), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient ponatinib as follows:

Ponatinib

Resolution of: 23 January 2014
Entry into force on: 23 January 2014
Federal Gazette, BAnz. [ ] No. [..] ; dd.mm.yyyy, p.[..]

Approved therapeutic indication

Iclusig® is indicated in adult patients with

- chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

1. Extent of the additional benefit of the medicinal product

Ponatinib is approved as a medicinal product for the treatment of rare diseases in accordance with 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 10 of German Social Code, Book Five (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). 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).

Extent of the additional benefit:

a) Adult patients with CML:

Non-quantifiable

b) Adult patients with Ph+ ALL:

Non-quantifiable

a) Adult patients with CML:

Study results according to endpoints:[1]

Ponatinib in chronic myeloid leukaemia (CML)[2]					
Chronic phase (CP)		**Accelerated phase (AP)**		**Blast crisis (BC)**	
R/I N = 203	**T315I N = 64**	**R/I N = 65**	**T315I N = 18**	**R/I N = 38**	**T315I N = 24**
Mortality					
Deaths n (%)					
12 (5.9 %)	5 (7.8 %)	8 (12.3 %)	4 (22.2 %)	26 (68.4 %)	17 (70.8 %)
Rate of overall survival (OS) after 12 months					
94.4%	90.2%	83.9%	72.2%	35.1%	16.0%
Median OS (weeks, min; max)					
n.a. (0.6; 72.1)	n.a. (6.4; 71.7)	n.a. (18.3; 79.9)	n.a. (18.4; 80.0)	26.6 (0.7; 66.0)	29.9 (1.7; 53.1)
Morbidity[3]					
Haematological response (HR): major haematologic response (MaHR)					
no data available	no data available	39 (60.0 %)	9 (50.0 %)	12 (31.6 %)	7 (29.2 %)
Cytogenetic response (CyR): major cytogenetic response (MCyR)					
99 (48.8 %)	45 (70.3 %)	22 (33.8 %)	10 (55.6 %)	7 (18.4 %)	7 (29.2 %)
- **Of which with complete cytogenetic response (CCyR)**					
76 (37.4 %)	42 (65.6 %)	13 (20.0 %)	6 (33.3 %)	6 (15.8 %)	5 (20.8 %)
Molecular response (MR): good molecular response (MMR)					
47 (23.2 %)	32 (50.0 %)	6 (9.2 %)	3 (16.7 %)	7 (18.4 %)	1 (4.2 %)
Progression-free survival (PFS)					
Number of patients with progression					
28 (13.8 %)	7 (10.9 %)	24 (36.9 %)	6 (33.3 %)	no data available	no data available
Median PFS (weeks, min; max)					
n.a. (0.1; 72.1)	n.a. (0.1; 60.0)	79.9 (6.0; 79.9)	n.a. (8.0; 80.0)	24.1 (0.3; 64.1)	21.4 (1.9; 36.9)

Health-related quality of life							
No quality of life data were collected in the AP24534-10-201 study.							
Chronic phase (CP)		**Accelerated phase (AP)**		**Blast crisis (BC)**		**Target population (total)**	
R/I N = 203	**T315I N = 64**	**R/I N = 65**	**T315I N = 18**	**R/I N = 38**	**T315I N = 24**	**R/I N = 306**	**T315I N = 106**
Side effects[4]							
Total rate of AE							
202 (99.5%)	63 (98.4%)	65 (100%)	17 (94.4%)	38 (100%)	24 (100%)	305 (99.7 %)	104 (98.1 %)
Total rate of SAE							
84 (41.4 %)	23 (35.9 %)	36 (55.4 %)	9 (50.0%)	31 (81.6 %)	20 (83.3 %)	151 (49.3 %)	52 (49.1 %)
AE of CTCAE grade 3 and 4							
163 (80.3 %)	37 (57.8 %)	48 (73.8 %)	10 (55.6 %)	16 (42.1 %)	11 (45.8 %)	227 (74.2 %)	58 (54.7 %)
Therapy discontinuations because of AE							
27 (13.3 %)	4 (6.3 %)	7 (10.8 %)	2 (11.1 %)	5 (13.2 %)	4 (16.7 %)	39 (12.7 %)	10 (9.4 %)
Frequent AE or AE of special interest							
Thrombocytopaenia (all grades)							
98 (48.3 %)	16 (25.0 %)	35 (53.8 %)	4 (22.2 %)	14 (36.8 %)	7 (29.2 %)	147 (48.0 %)	27 (25.5 %)
Thrombocytopaenia CTCAE grade 3 and 4							
77 (37.9 %)	12 (18.8 %)	29 (44.6 %)	3 (16.7 %)	13 (34.2 %)	7 (29.2 %)	119 (38.9 %)	22 (20.8 %)
Pancreatitis (all grades)							
14 (6.9 %)	5 (7.8 %)	5 (7.7 %)	0	2 (5.3 %)	1 (4.2 %)	21 (6.9 %)	6 (5.7 %)
Pancreatitis CTCAE grade 3 and 4							
12 (5.9 %)	5 (7.8 %)	3 (4.6 %)	0	2 (5.3%)	0	17 (5.6 %)	5 (4.7 %)

Abbreviations used: CTCAE = Common Terminology Criteria for Adverse Events; n.a. = not achieved (by the data cut-off of 27 April 2012); N = total number of patients with data on the corresponding endpoint; R/I = resistant or intolerant to dasatinib or nilotinib; (S)AE = (serious) adverse event; T315I = Mutation by replacement of threonine by isoleucine at Abelson amino acid position 315.

[1] Data for the target population of the study from the benefit assessment of the G-BA and the dossier of the pharmaceutical company. Data cut-off of 27 April 2012.

[2] Five patients with CML (three with CP-CML and two with AP-CML) could not be assigned to a cohort because despite documented positive T315I history. no T315I mutation could be detected. These patients were not considered in this presentation of the study cohorts.
[3] Number of patients with event
[4] Specified as the number of patients with at least one corresponding AE.

b) Adult patients with Ph+ ALL:

Study results according to endpoints:[5]

Ponatinib in Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL)	
R/I **N = 10**	**T315I** **N = 22**
Mortality	
Deaths n (%)	
5 (50.0 %)	12 (54.5 %)
Rate of overall survival (OS) after 12 months	
50.0%	39.0%
Median OS (weeks, min; max)	
n.a. (7.7; 57.0)	28.4 (0.4; 58.7)
Morbidity[6]	
Haematological response (HR): major haematologic response (MaHR)	
5 (50 %)	8 (36.4 %)
Cytogenetic response (CyR): major cytogenetic response (MCyR)	
6 (60.0 %)	9 (40.9 %)
- **Of which with complete cytogenetic response (CCyR)**	
5 (50.0 %)	7 (31.8 %)
Molecular response (MR): good molecular response (MMR)	
2 (20.0 %)	1 (4.5 %)
Progression-free survival (PFS)	
Number of patients with progression	
no data available	no data available
Median PFS (weeks, min; max)	
17.0 weeks (4.3; 36.0)	12.4 weeks (0.1; 46.1)
Health-related quality of life	

No quality of life data were collected in the AP24534-10-201 study.

R/I N = 10	T315I N = 22	Target population (total) N = 32
Side effects[7]		
Total rate of AE		
10 (100 %)	22 (100 %)	32 (100 %)
Total rate of SAE		
7 (70.0 %)	16 (72.7 %)	23 (71.9 %)
AE of CTCAE grade 3 and 4		
8 (80.0 %)	12 (54.5 %)	20 (62.5 %)
Therapy discontinuations because of AE		
0	1 (4.5 %)	1 (3.1 %)
Frequent AE or AE of special interest		
Thrombocytopaenia		
3 (30.0 %)	1 (4.5 %)	4 (12.5 %)
Thrombocytopaenia CTCAE grade 3 and 4		
3 (30.0 %)	1 (4.5 %)	4 (12.5 %)
Pancreatitis		
0	0	0
Pancreatitis CTCAE grade 3 and 4		
0	0	0

Abbreviations used: CTCAE = Common Terminology Criteria for Adverse Events; n.a. = not achieved (by the data cut-off of 27 April 2012); N = total number of patients with data on the corresponding endpoint; R/I = resistant or intolerant to dasatinib or nilotinib; (S)AE = (serious) adverse event; T315I = Mutation by replacement of threonine by isoleucine at Abelson amino acid position 315.

[5] Data for the target population of the study from the benefit assessment of the G-BA and the dossier of the pharmaceutical company. Data cut-off of 27 April 2012.

[6] Number of patients with event

[7] Specified as the number of patients with at least one corresponding AE.

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

a) Adult patients with CML:

Target population: approx. 500 to 940 patients

b) Adult patients with Ph+ ALL:

Target population: approx. 25 to 195 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 Iclusig® (active ingredient: ponatinib) at the following publicly accessible link (last access: 10 December 2013):
http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002695/WC500145646.pdf

In November 2013, the EMA reported an increased incidence of thrombotic events as part of further evaluations of ongoing clinical studies on ponatinib. In the written statement of the EMA dated 6 December 2013 regarding thrombotic events in connection with treatment with ponatinib, it is stated that a final risk assessment will take place in 2014. The EMA will update the summary of product characteristics as appropriate. Consequently, the status of the product information in particular must be checked to ensure that it is up to date. Any changes must be taken into account.

Treatment with ponatinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with CML and Ph+ ALL.

4. Treatment costs

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration/treatment (days)	Treatment days per patient per year
Ponatinib	1 × 45 mg daily	continuous	365	365

Usage and consumption:

Designation of the therapy	Potency (mg)[8]	Quantity per package (film-coated tablets)	Average annual consumption (film-coated tablets)
Ponatinib	45	30	365

[8] The potency of 45 mg is considered according to the recommended dose (45 mg once daily).

Costs:

Costs of the medicinal product:

Designation of the therapy	Costs (pharmacy sales price)	Costs after deduction of statutory rebates
Ponatinib	€ 7,350.24	€ 6,991.44 [€ 1.80[9]; € 357.00[10]]

[9] Rebate according to Section 130 SGB V.
[10] Rebate according to Section 130a SGB V.

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 January 2014

Costs for additionally required SHI services:

not applicable

Annual treatment costs:

Designation of the therapy	Annual treatment costs per patient
Ponatinib	€ 85,062.52

II. Entry into force

1. **The resolution will enter into force with effect from the day of its publication on the internet on the website of the Federal Joint Committee on 23 January 2014.**
2. **The period of validity of the resolution is limited to 1 February 2015.**

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

Berlin, 23 January 2014

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

Hecken