Resolution

Gemeinsamer Bundesausschuss

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

of 20 November 2020

At its session on 20 November 2020, the Federal Joint Committee (G-BA) 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 DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII will be amended as follows:

1. The information on ponatinib as amended by the resolution of 23 January 2014 (Federal Gazette, BAnz AT 14 February 2014 B2) as last amended on 17 October 2019 is hereby repealed.

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

Ponatinib

Resolution of: 20 November 2020
Entry into force on: 20 November 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 1 July 2013):

Iclusig is indicated in adult patients with 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 and significance of the evidence

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. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence 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) 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).

Adult patients with 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.

Extent of the additional benefit and significance of the evidence for ponatinib:

Hint for a non-quantifiable additional benefit because the scientific data does not permit quantification.

Study results according to endpoints:[1]

PACE study: single-arm, multi-centre, open-label Phase II study

Adult patients with 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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	not assessable
Morbidity	n.a.	not assessable
Health-related quality of life	∅	No data available.
Side effects	n.a.	not assessable

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

Mortality

Endpoint	R/I		T315I mutation		Total	
	N	Median survival time in weeks [95% CI][b] *Patients with event n (%)* [a]	N	Median survival time in weeks [95% CI][b] *Patients with event n (%)* [a]	N	Median survival time in weeks [95% CI][b] *Patients with event n (%)* [a]
Overall survival						
PACE	10	56.5 [7.7–108.1] 8 (80.0%)	22	28.4 [17.0–57.3] 17 (77.3)	32	33.1 [19.0–65.4] 25 (78.1)

Morbidity

No relevant data are available.

Health-related quality of life

[1] Data from the dossier assessment by the G-BA (published on 1 September 2020) unless otherwise indicated.

No quality of life data were collected.

Side effects

Results from the PACE study, safety population[c]:

Endpoint	R/I		T315I mutation		Total	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Adverse events in total						
	10	10 (100%)	22	22 (100%)	32	32 (100%)
Serious adverse events (SAE)						
	10	8 (80.0)	22	17 (77.3)	32	25 (78.1)
Severe adverse events (CTCAE grade ≥ 3)						
	10	9 (90.0)	22	19 (86.4)	32	28 (87.5)
Therapy discontinuation because of adverse events [d]						
	10	1 (10.0)	22	2 (9.1)	32	3 (9.4)
Adverse events of special interest (AESI)						
Arterial occlusions	10	1 (10.0)	22	2 (9.1)	32	3 (9.4)
Cardiovascular occlusion events	10	0	22	1 (4.5)	32	1 (3.1)
Cerebro-vascular occlusion events	10	0	22	1 (4.5)	32	1 (3.1)
Peripheral arterial vascular occlusions	10	1 (10.0)	22	2 (9.1)	32	3 (9.4)
Venous thrombosis/venous embolisms	0	0	22	3 (13.6)	32	3 (9.4)
Vascular occlusions	10	1 (10.0)	22	5 (22.7)	32	6 (18.8)
Liver toxicity	10	2 (20.0)	22	3 (13.6)	32	5 (15.6)
Heart failure	10	0	22	2 (9.1)	32	2 (6.3)
Skin and subcutaneous tissue disorders	10	6 (60.0)	22	13 (59.1)	32	19 (59.4)
Infections and infestations	10	8 (80.0)	22	15 (68.2)	32	23 (71.9)
Myelosuppression	10	8 (80.0)	22	11 (50.0)	32	19 (59.4)
Oedema and fluid retention	10	7 (70.0)	22	6 (27.3)	32	13 (40.6)
Hypertension	10	3 (30.0)	22	5 (22.7)	32	8 (25.0)
Endpoint	**R/I**		**T315I mutation**		**Total**	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*

Eye diseases	10	4 (40.0)	22	5 (22.7)	32	9 (28.1)
Bleedings	10	3 (30.0)	22	7 (31.8)	32	10 (31.3)
Pancreatitis	10	2 (20.0)	22	1 (4.5)	32	3 (9.4)
Chemical pancreatitis	10	2 (20.0)	22	1 (4.5)	32	3 (9.4)
Cardiac arrhythmia	10	3 (30.0)	22	5 (22.7)	32	8 (25.0)
Prolongation of the QT interval	10	1 (10.0)	22	1 (4.5)	32	2 (6.3)

[a] Based on the treated population; until the end of the study (data cut-off of 6 February 2017)
[b] Clopper-Pearson
[c] All patients who have experienced at least 1 event.
[d] Study participants received the study medication until the onset of disease progression, unacceptable AE, or withdrawal of consent, whichever occurred earlier.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; MMR = major molecular response; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; OS = overall survival; Ph+ ALL = Philadelphia chromosome positive acute lymphoblastic leukaemia; PT = preferred terms; R/I: resistant or intolerant; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

SAE and severe AE (CTCAE ≥ 3) with incidence ≥ 5%

Endpoint	**Ph+ ALL**	
	N	*Patients with event n (%)*
Serious AE (SAE) with incidence ≥ 5%(SOC)		
Cardiac disorders	32	7 (21.9)
Atrial fibrillation	32	4 (12.5)
Vascular disorders	32	5 (15.6)
Infections and infestations	32	10 (31.3)
Sepsis	32	2 (6.3)
Septic shock	32	2 (6.3)
Gastrointestinal disorders	32	6 (18.8)
Endpoint	**Ph+ ALL**	
	N	*Patients with event n (%)*
Benign, malignant and unspecified neoplasms	32	5 (15.6)
Progression	32	4 (12.5)

Respiratory, thoracic and mediastinal disorders	32	2 (6.3)
Blood and lymphatic system disorders	32	8 (25.0)
Febrile neutropoenia	32	7 (21.9)
Metabolism and nutrition disorders	32	3 (9.4)
Dehydration	32	2 (6.3)
Severe AE (CTCAE grade ≥ 3) with incidence ≥ 5% (SOC)		
Infections and infestations	32	14 (43.8)
Investigations	32	13 (40.6)
Neutropoenia	32	7 (21.9)
Thrombocytopoenia	32	6 (18.8)
Blood and lymphatic system disorders	32	13 (40.6)
Anaemia	32	6 (18.8)
Febrile neutropoenia	32	8 (25.0)
Metabolism and nutrition disorders	32	7 (21.9)
Gastrointestinal disorders	32	7 (21.9)
Vascular disorders	32	6 (18.8)
Benign, malignant and unspecified neoplasms	32	5 (15.6)
Respiratory, thoracic and mediastinal disorders	32	4 (12.5)
Cardiac disorders	32	4 (12.5)
General disorders and administration site conditions	32	3 (9.4)
Skin and subcutaneous tissue disorders	32	2 (6.3)
Musculoskeletal and connective tissue disorders	32	2 (6.3)
Endpoint	**Ph+ ALL**	
	N	*Patients with event n (%)*
Hepatobiliary diseases	32	2 (6.3)

Abbreviations used:
Ph+ ALL = Philadelphia chromosome positive acute lymphoblastic leukaemia; PT = preferred terms; SOC = system organ class

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

Adult patients with 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

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: 3 September 2020):

https://www.ema.europa.eu/documents/product-information/iclusig-epar-product-information_de.pdf

Treatment with ponatinib should be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL).

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide information for healthcare professionals on ponatinib in a suitable form, in particular on the importance of the risk assessment of patients before starting treatment with ponatinib; on data on the relationship between dosage and the risk of vascular occlusion; on recommendations for close monitoring when a dose reduction is applied; on recommendations to discontinue treatment if no complete haematological response has occurred within 3 months of treatment; on major side effects for which monitoring and/or dose adjustment is recommended (according to SmPC: pancreatitis, increased amylase and lipase levels, myelosuppression, abnormalities in liver function tests, bleeding, cardiac disorders/left ventricular dysfunction, vascular occlusion, hypertension); on instructions for side effect management based on monitoring and dose modification or treatment discontinuation.

4. Treatment costs

Annual treatment costs:

Adult patients with 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

Designation of the therapy	Annual treatment costs/patient
Ponatinib	€ 74,755.04

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 20 November 2020.

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

Berlin, 20 November 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken