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: Chronic Myeloid 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of 23 January 2014 (Federal Gazette, BAnz AT 14 February 2014 B2) as last amended on 17 October 2019 is hereby repealed.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 June 2013):

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.

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 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

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

OPTIC study: multi-centre, randomised Phase II study (Data cut-off of 20 July 2019)[2]

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

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	n.a.	not assessable
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

[1] Data from the dossier assessment by the G-BA (published on 1 September 2020) unless otherwise indicated.
[2] For the benefit assessment, only the treatment arm with 45 mg ponatinib/day can be considered because the doses in the other two arms do not comply with the requirements in the product information.

Study results: chronic phase

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	203	n.a. 41 (20.2%)	64	n.a. 18 (28.1)	267	n.a. 59 (22.1)
OPTIC[3]	Separate evaluations for R/I and T315I mutation are not available				94	n.e. 5 (5.3)

Morbidity

Endpoint	R/I		T315I mutation		Total	
	N	Median time to event in weeks [95% CI] *Patients with event n (%) [a]*	N	Median time to event in weeks [95% CI] *Patients with event n (%) [a]*	N	Median time to event in weeks [95% CI] *Patients with event n (%) [a]*
Major molecular response (MMR)						
PACE	203	n.a. [108.0; n.a.] 71 (35.0)	64	n.a. [97.9; n.a.] 37 (57.8)	267	n.a. [223.0; n.a.] 108 (40.4)
OPTIC	In the present evaluation of the OPTIC study, only the achievement of an MMR from month 3 and then every further three months until month 36 was documented.					

Health-related quality of life

PACE study:

No quality of life data were collected.

OPTIC study:

No relevant data are available.

[3] The duration of the follow-up of CP-CML patients to the data cut-off presented in the OPTIC study is significantly shorter than the duration of the follow-up of CP-CML patients in the PACE study (OPTIC: median 21.0 months; PACE: median 56.8 months).

Side effects

Results from the PACE and OPTIC studies, safety population[c]:

Endpoint	R/I		T315I mutation		Total	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N[d]	*Patients with event n (%)*
Adverse events in total						
PACE	203	203 (100%)	64	64 (100%)	270	270 (100%)
OPTIC[4]	Separate evaluations for R/I and T315I mutation are not available				94	92 (97.9%)
Serious adverse events (SAE)						
PACE	203	131 (64.5)	64	39 (60.9)	270	171 (63.3)
OPTIC[4]	Separate evaluations for R/I and T315I mutation are not available				94	29 (30.9)
Severe adverse events (CTCAE grade ≥ 3)						
PACE	203	188 (92.6)	64	50 (78.1)	270	239 (88.5)
OPTIC[4]	No information available.					
Therapy discontinuations because of adverse events[e]						
PACE	203	45 (22.2)	64	11 (17.2)	270	57 (21.1)
OPTIC[4]	Separate evaluations for R/I and T315I mutation are not available				94	13 (13.8)
Adverse events of special interest (AESI)						
Arterial occlusions	203	57 (28.1)	64	26 (40.6)	270	84 (31.1)
Cardiovascular occlusion events	203	27 (13.3)	64	15 (23.4)	270	42 (15.6)
Cerebro-vascular occlusion events	203	23 (11.3)	64	12 (18.8)	270	35 (13.0)
Peripheral arterial vascular occlusions	203	26 (12.8)	64	11 (17.2)	270	38 (14.1)
Venous thrombosis/venous embolisms	203	11 (5.4)	64	4 (6.3)	270	15 (5.6)
Vascular occlusions	203	63 (31.0)	64	28 (43.8)	270	92 (34.1)
Liver toxicity	203	58 (28.6)	64	20 (31.3)	270	78 (28.9)
Heart failure	203	16 (7.9)	64	6 (9.4)	270	22 (8.1)
Skin and subcutaneous tissue disorders	203	165 (81.3)	64	55 (85.9)	270	223 (82.6)

[4] The duration of the ponatinib exposure of CP-CML patients at the data cut-off presented in the OPTIC study is significantly shorter than the duration of ponatinib exposure of CP-CML patients in the PACE study (OPTIC: median 392.0 days; PACE: median 978.5 days).

Endpoint	R/I		T315I mutation		Total	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N[d]	*Patients with event n (%)*
Infections and infestations	203	129 (63.5)	64	39 (60.9)	270	171 (63.3)
Myelosuppression	203	122 (60.1)	64	26 (40.6)	270	148 (54.8)
Oedema and fluid retention	203	63 (31.0)	64	16 (25.0)	270	79 (29.3)
Hypertension	203	77 (37.9)	64	21 (32.8)	270	100 (37.0)
Eye diseases	203	66 (32.5)	64	21 (32.8)	270	87 (32.2)
Bleedings	203	49 (24.1)	64	11 (17.2)	270	61 (22.6)
Pancreatitis	203	69 (34.0)	64	17 (26.6)	270	86 (31.9)
Clinical pancreatitis	203	16 (7.9)	64	5 (7.8)	270	21 (7.8)
Chemical pancreatitis	203	61 (30.0)	64	16 (25.0)	270	77 (28.5)
Cardiac arrhythmia	203	43 (21.2)	64	9 (14.1)	270	52 (19.3)
Prolongation of the QT interval	203	13 (6.4)	64	4 (6.3)	270	17 (6.3)
Hypothyroidism	203	7 (3.4)	64	2 (3.1)	270	9 (3.3)

[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] 3 study participants in the CP-CML were not assigned to any cohort.
[e] Study participants received the study medication until the onset of disease progression, unacceptable AE, or withdrawal of consent, whichever occurred earlier. These possible reasons for therapy discontinuation, which can occur before a potential discontinuation because of AE, thus represent a competing event, which limits the certainty of results and the interpretability of the rates.

Abbreviations used:
AD = absolute difference; CML = chronic myeloid leukaemia; CP = chronic phase; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.s. = not specified; n.c. = not calculable; n.a. = not achieved; R/I = resistant or intolerant; SAE = serious adverse event(s); AE = adverse event(s); vs = versus

Study results: accelerated phase

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	65	241.3 [138.4; n.a.] 30 (46.2)	18	263.9 [40.1–306.1] 9 (50.0)	83	241.3 [140; n.a.] 39 (47.0)

Morbidity

Endpoint	R/I		T315I mutation		Total	
	N	Median time to event in weeks [95% CI][b] *Patients with event n (%) [a]*	N	Median time to event in weeks [95% CI][b] *Patients with event n (%) [a]*	N	Median time to event in weeks [95% CI][b] *Patients with event n (%) [a]*
Major molecular response (MMR)						
PACE	65	80.0 [8.1; n.a.] 12 (18.5)	18	31.7 [16.0; n.a.] 6 (33.3)	83	58.1 [20.3; n.a.] 18 (21.7)

Health-related quality of life

Endpoints on quality of life were not collected in the PACE study.

Side effects

Results from the PACE study[c]:

Endpoint	R/I		T315I mutation		Total	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N[d]	*Patients with event n (%)*
Adverse events in total						
	65	65 (100%)	18	18 (100%)	85	85 (100%)
Serious adverse events (SAE)						
	65	44 (67.7)	18	13 (72.2)	85	59 (69.4)
Severe adverse events (CTCAE grade ≥ 3)						
	65	60 (92.3)	18	16 (88.9)	85	78 (91.8)
Therapy discontinuations because of adverse events[e]						
	65	7 (10.8)	18	2 (11.1)	85	10 (11.8)
Adverse events of special interest (AESI)						
Arterial occlusions	65	11 (16.9)	18	5 (27.8)	85	17 (20.0)
Cardiovascular occlusion events	65	8 (12.3)	18	3 (16.7)	85	12 (14.1)
Cerebro-vascular occlusion events	65	3 (4.6)	18	2 (11.1)	85	5 (5.9)
Peripheral arterial vascular occlusions	65	3 (4.6)	18	2 (11.1)	85	5 (5.9)
Venous thrombosis/venous embolisms	65	2 (3.1)	18	1 (5.6)	85	3 (3.5)
Vascular occlusions	65	13 (20.0)	18	5 (27.8)	85	19 (22.4)
Liver toxicity	65	25 (38.5)	18	6 (33.3)	85	31 (36.5)
Heart failure	65	3 (4.6)	18	2 (11.1)	85	6 (7.1)
Skin and subcutaneous tissue disorders	65	52 (80.0)	18	14 (77.8)	85	68 (80.0)
Infections and infestations	65	49 (75.4)	18	15 (83.3)	85	65 (76.5)
Myelosuppression	65	48 (73.8)	18	10 (55.6)	85	60 (70.6)
Oedema and fluid retention	65	22 (33.8)	18	7 (38.9)	85	30 (35.3)
Hypertension	65	14 (21.5)	18	8 (44.4)	85	22 (25.9)
Eye diseases	65	21 (32.3)	18	6 (33.3)	85	28 (32.9)
Bleedings	65	28 (43.1)	18	3 (16.7)	85	32 (37.6)
Pancreatitis	65	16 (24.6)	18	3 (16.7)	85	19 (22.4)
Endpoint	**R/I**		**T315I mutation**		**Total**	

	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N[d]	*Patients with event n (%)*
Clinical pancreatitis	65	7 (10.8)	18	0	85	7 (8.2)
Chemical pancreatitis	65	13 (20.0)	18	3 (16.7)	85	16 (18.8)
Cardiac arrhythmia	65	12 (18.5)	18	1 (5.6)	85	14 (16.5)
Prolongation of the QT interval	65	5 (7.7)	18	0	85	5 (5.9)
Hypothyroidism	65	4 (6.2)	18	0	85	4 (4.7)
Tumour lysis syndrome	65	1 (1.5)	18	1 (5.6)	85	2 (2.4)

[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] 2 study participants in the AP-CML were not assigned to any cohort.
[e] Study participants received the study medication until the onset of disease progression, unacceptable AE, or withdrawal of consent, whichever occurred earlier. These possible reasons for therapy discontinuation, which can occur before a potential discontinuation because of AE, thus represent a competing event, which limits the certainty of results and the interpretability of the rates.

Abbreviations used:
AD = absolute difference; CML = chronic myeloid leukaemia; CTCAE = Common Terminology Criteria for Adverse Events; 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; R/I = resistant or intolerant; SAE = serious adverse event(s); AE = adverse event(s); vs = versus

Study results: Blast phase

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	38	26.6 [14.1–54.1] 32 (84.2%)	24	29.9 [14.9–46.1] 22 (91.7)	62	29.9 [17.0–40.6] 54 (87.1)

Morbidity

Endpoint	R/I		T315I mutation		Total	
	N	Median time to event in weeks [95% CI][b] *Patients with event n (%)* [a]	N	Median time to event in weeks [95% CI][b] *Patients with event n (%)* [a]	N	Median time to event in weeks [95% CI][b] *Patients with event n (%)* [a]
Major molecular response (MMR)						
PACE	38	n.a. [5.9; n.a.] 7 (18.4)	24	14.0 [n.s.] 1 (4.2)	62	n.a. [5.9; n.a.] 8 (12.9)

Health-related quality of life

Endpoints on quality of life were not collected in the PACE study.

Side effects

Results from the PACE study[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						
	38	38 (100%)	24	24 (100%)	62	62 (100%)
Serious adverse events (SAE)						
	38	33 (86.8)	24	20 (83.3)	62	53 (85.5)
Severe adverse events (CTCAE grade ≥ 3)						
	38	37 (97.4)	24	21 (87.5)	62	58 (93.5)
Therapy discontinuation because of adverse events [d]						
	38	5 (13.2)	24	4 (16.7)	62	9 (14.5)
Adverse events of special interest (AESI)						
Arterial occlusions	38	7 (18.4)	24	0	62	7 (11.3)
Cardiovascular occlusion events	38	4 (10.5)	24	0	62	4 (6.5)
Peripheral arterial vascular occlusions	38	2 (5.3)	24	0	62	2 (3.2)
Venous thrombosis/venous embolisms	38	4 (10.5)	24	2 (8.3)	62	6 (9.7)
Endpoint	**R/I**		**T315I mutation**		**Total**	

	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Vascular occlusions	38	9 (23.7)	24	2 (8.3)	62	11 (17.7)
Liver toxicity	38	13 (34.2)	24	7 (29.2)	62	20 (32.3)
Heart failure	38	7 (18.4)	24	2 (8.3)	62	9 (14.5)
Skin and subcutaneous tissue disorders	38	25 (65.8)	24	18 (75.0)	62	43 (69.4)
Infections and infestations	38	23 (60.5)	24	12 (50.0)	62	35 (56.5)
Myelosuppression	38	26 (68.4)	24	16 (66.7)	62	42 (67.7)
Oedema and fluid retention	38	16 (42.1)	24	4 (16.7)	62	20 (32.3)
Hypertension	38	11 (28.9)	24	3 (12.5)	62	14 (22.6)
Eye diseases	38	8 (21.1)	24	4 (16.7)	62	12 (19.4)
Bleedings	38	13 (34.2)	24	10 (41.7)	62	23 (37.1)
Pancreatitis	38	9 (23.7)	24	3 (12.5)	62	12 (19.4)
Clinical pancreatitis	38	2 (5.3)	24	1 (4.2)	62	3 (4.8)
Chemical pancreatitis	38	7 (18.4)	24	2 (8.3)	62	9 (14.5)
Cardiac arrhythmia	38	8 (21.1)	24	7 (29.2)	62	15 (24.2)
Prolongation of the QT interval	38	1 (2.6)	24	1 (4.2)	62	2 (3.2)
Hypothyroidism	38	1 (2.6)	24	0	62	1 (1.6)
Tumour lysis syndrome	38	1 (2.6)	24	0	62	1 (1.6)

[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. These possible reasons for therapy discontinuation, which can occur before a potential discontinuation because of AE, thus represent a competing event, which limits the certainty of results and the interpretability of the rates.

Abbreviations used:
AD = absolute difference; CML = chronic myeloid leukaemia; BP= blast phase; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.s. = not specified; n.c. = not calculable; n.a. = not achieved; R/I = resistant or intolerant; SAE = serious adverse event(s); AE = adverse event(s); vs = versus

SAE and severe AE (CTCAE ≥ 3) with incidence ≥ 5% in the chronic, accelerated and blast phase

Results from the PACE and OPTIC studies:

Endpoint	**CP-CML**		**AP-CML**		**BP-CML**	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Serious AE (SAE) with incidence ≥ 5%						
Cardiac disorders	270	56 (20.7)	85	11 (12.9)	62	11 (17.7)
Atrial fibrillation	270	15 (5.6)	85	0	62	1 (1.6)
OPTIC[4]	94	6 (6.4)	-	-	-	-
Vascular disorders	270	44 (16.3)	85	9 (10.6)	62	5 (8.1)
Infections and infestations	270	42 (15.6)	85	29 (34.1)	62	19 (30.6)
Pneumonia	270	15 (5.6)	85	9 (10.6)	62	8 (12.9)
Gastrointestinal disorders	270	40 (14.8)	85	16 (18.8)	62	14 (22.6)
OPTIC[4]	94	5 (5.3)	-	-	-	-
Pancreatitis	270	19 (7.0)	85	5 (5.9)	62	2 (3.2)
Nervous system disorders	270	39 (14.4)	85	14 (16.5)	62	6 (9.7)
Benign, malignant and unspecified neoplasms	270	27 (10.0)	85	17 (20.0)	62	22 (35.5)
Progression	270	8 (3.0)	85	11 (12.9)	62	18 (29.0)
Investigations	270	19 (7.0)	85	9 (10.6)	62	7 (11.3)
General disorders and administration site conditions	270	24 (8.9)	85	13 (15.3)	62	7 (11.3)
OPTIC[4]	94	8 (8.5)	-	-	-	-
Pyrexia	270	8 (3.0)	85	8 (9.4)	62	3 (4.8)
Respiratory, thoracic and mediastinal disorders	270	15 (5.6)	85	8 (9.4)	62	8 (12.9)
Blood and lymphatic system disorders	270	13 (4.8)	85	8 (9.4)	62	12 (19.4)
OPTIC[4]	94	7 (7.4)	-	-	-	-
Endpoint	**CP-CML**		**AP-CML**		**BP-CML**	

	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Anaemia	270	8 (3.0)	85	4 (4.7)	62	5 (8.1)
Injury, poisoning, and procedural complications	270	10 (3.7)	85	6 (7.1)	62	no data available
Metabolism and nutrition disorders	270	13 (4.8)	85	5 (5.9)	62	4 (6.5)
Musculoskeletal and connective tissue disorders	270	8 (3.0)	85	4 (4.7)	62	4 (6.5)
Severe AE (CTCAE ≥ 3) with incidence ≥ 5% (PACE)						
Investigations	270	149 (55.2)	85	57 (67.1)	62	37 (59.7)
Thrombocytopoenia	270	95 (35.2)	85	37 (43.5)	62	22 (35.5)
Neutropoenia	270	45 (16.7)	85	31 (36.5)	62	18 (29.0)
Gastrointestinal disorders	270	63 (23.3)	85	18 (21.2)	62	14 (22.6)
Skin and subcutaneous tissue disorders	270	30 (11.1)	85	15 (17.6)	62	5 (8.1)
Musculoskeletal and connective tissue disorders	270	32 (11.9)	85	7 (8.2)	62	3 (4.8)
General disorders and administration site conditions	270	23 (8.5)	85	12 (14.1)	62	11 (17.7)
Nervous system disorders	270	40 (14.8)	85	13 (15.3)	62	7 (11.3)
Infections and infestations	270	42 (15.5)	85	27 (31.8)	62	19 (30.6)
Vascular disorders	270	61 (22.6)	85	15 (17.7)	62	10 (16.1)
Hypertension	270	37 (13.7)	85	9 (10.6)	62	5 (8.1)
Respiratory, thoracic and mediastinal disorders	270	20 (7.4)	85	9 (10.6)	62	9 (14.5)
Metabolism and nutrition disorders	270	40 (14.8)	85	10 (11.8)	62	12 (19.4)
Cardiac disorders	270	49 (17.5)	85	8 (9.4)	62	14 (22.6)
Endpoint	**CP-CML**		**AP-CML**		**BP-CML**	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	N	*Patients with event n (%)*
Blood and lymphatic system disorders	270	36 (13.3)	85	23 (27.1)	62	27 (43.5)

Anaemia	270	28 (10.4)	85	19 (22.4)	62	20 (32.2)
Injury, poisoning, and procedural complications	270	6 (2.3)	85	6 (7.1)	62	2 (3.2)
Benign, malignant and unspecified neoplasms	270	19 (7.0)	85	15 (17.7)	62	23 (37.1)
Progression	270	8 (3.0)	85	11 (12.9)	62	19 (30.6)
Hepatobiliary diseases	270	10 (3.7)	85	5 (5.9)	62	4 (6.4)
Abbreviations used: AP = accelerated phase; BP = blast phase; CML = chronic myeloid leukaemia; CP = chronic phase; PT = preferred term(s); SOC = system organ class(es)						

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

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

approx. 500 to 940 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 chronic myeloid leukaemia (CML).

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 factors to be considered when considering dose reduction in CP-CML patients with good cytogenetic response (MCyR) without side effects; 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 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

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