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: Ripretinib (gastrointestinal stromal tumours (GIST), ≥ 3 prior therapies)

of 16 June 2022

At its session on 16 June 2022, 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

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

Ripretinib

Resolution of: 16 June 2022
Entry into force on: 16 June 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 18 November 2021):

QINLOCK is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

Therapeutic indication of the resolution (resolution of 16 June 2022):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Ripretinib 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 11, 1st half of the sentence 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).

<u>Adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib</u>

Extent of the additional benefit and significance of the evidence of ripretinib:

Hint for a major additional benefit

Study results according to endpoints:[1]

Adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantage in health status
Health-related quality of life	↑	Advantage in physical functioning and role functioning
Side effects	↑	Overall advantage in therapeutic benefit. The results for the endpoints can only be interpreted to a limited extent.
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		

INVICTUS study

Study design: double-blind, placebo-controlled, phase III study
double-blind phase followed by open-label extension phase

Comparison: Ripretinib + Best Supportive Care (BSC) vs placebo + BSC (2:1)

Data cut-off: 2. data cut-off of 10 August 2020

[1] Data from the dossier assessment of the G-BA (published on 1. April 2022), and from the amendment to the dossier assessment, unless otherwise indicated.

Mortality

Endpoint	Ripretinib + BSC		Placebo + BSC		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 (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
Overall survival					
	85	79.1 [57.1; n.c.] *44 (51.8)*	44	27.4 [17.9; 43.4] *35 (79.5)*	0.42 [0.27; 0.67] < 0.001 AD: + 51.7 weeks

Morbidity

Endpoint	Ripretinib + BSC		Placebo + BSC		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value [a] Absolute difference (AD)[b]
Progression-free survival (PFS)[c]					
	85	27.571 [20.000; 35.286] *68 (80.00)*	44	4.143 [4.000; 7.286] *37 (84.09)*	0.165 [0.100; 0.270] < 0.0001 AD: + 23.4 weeks
Disease symptomatology (EORTC QLQ-C30) – time to first deterioration[d]					
Fatigue	85	4.1 [2.4; 8.0] *60 (70.6)*	44	2.6 [2.1; 6.9] *34 (77.3)*	0.77 [0.50; 1.18] 0.229
Nausea and vomiting	85	12.1 [4.4; 20.1] *53 (62.4)*	44	9.4 [5.0; 19.6] *29 (65.9)*	1.00 [0.64; 1.58] 0.992
Pain	85	8.1 [4.3; 20.4] *48 (56.5)*	44	7.3 [4.1; 10.1] *29 (65.9)*	0.74 [0.47; 1.18] 0.208
Dyspnoea	85	20.1 [11.9; 32.1] *48 (56.5)*	44	10.1 [6.9; 37.0] *24 (54.6)*	0.87 [0.53; 1.42] 0.577

(continuation)

Endpoint	**Ripretinib + BSC**		**Placebo + BSC**		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value [a] Absolute difference (AD)[b]
Appetite loss	85	16.1 [8.1; 24.1] *52 (61.2)*	44	7.0 [4.1; 11.7] *30 (68.2)*	0.72 [0.46; 1.13] 0.157
Insomnia	85	16.3 [4.4; 36.3] *47 (55.3)*	44	7.6 [4.1; 17.0] *27 (61.4)*	0.74 [0.46; 1.19] 0.209
Constipation	85	8.3 [8.0; 20.1] *50 (58.8)*	44	9.0 [4.1; 27.6] *25 (56.8)*	0.97 [0.60; 1.57] 0.911
Diarrhoea	85	21.1 [12.0; 32.1] *48 (56.5)*	44	27.3 [13.1; n.c.] *17 (38.6)*	1.41 [0.81; 2.44] 0.229
Health status (EQ-5D VAS) – time to first deterioration[e]					
	85	35.0 [20.3; 89.9] *38 (44.7)*	44	6.9 [4.1; 18.0] *27 (61.4)*	0.49 [0.30; 0.81] 0.005 AD: + 28.1 weeks

Health-related quality of life

Endpoint	**Ripretinib + BSC**		**Placebo + BSC**		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value [a] Absolute difference (AD)[b]
Global health status and functional scales (EORTC QLQ-C30) - time to first deterioration[f]					
Global health status	85	22.3 [4.4; 56.3] *40 (47.1)*	44	n.a. [54.4; n.c.] *10 (22.7)*	2.17 [1.09; 4.30] 0.027 AD: n.a.
Physical functioning	85	28.3 [12.0; 52.4] *48 (56.5)*	44	7.3 [4.0; 12.6] *32 (72.7)*	0.52 [0.33; 0.81] 0.004 AD: + 21.0 weeks
Role functioning	85	12.7 [8.1; 20.3] *52 (61.2)*	44	4.6 [4.0; 7.0] *33 (75.0)*	0.49 [0.31; 0.77] 0.002 AD: + 8.1 weeks
Cognitive functioning	85	20.3 [12.0; 36.4] *49 (57.7)*	44	7.3 [4.1; 18.9] *27 (61.4)*	0.72 [0.45; 1.15] 0.170
Emotional functioning	85	24.4 [11.9; 40.1] *47 (55.3)*	44	10.0 [5.0; 24.1] *25 (56.8)*	0.75 [0.46; 1.21] 0.237
Social functioning	85	16.1 [8.4; 29.0] *52 (61.2)*	44	7.9 [4.1; 16.1] *28 (63.6)*	0.65 [0.41; 1.03] 0.067

Side effects

Endpoint	Ripretinib + BSC		Placebo + BSC		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N[g]	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[h] Absolute difference (AD)[b]
Total adverse events - presented additionally					
	85	84 (98.8)	43	42 (97.7)	-
Severe AEs (CTCAE grade ≥ 3)					
	85	28.00 [12.86; 41.86] *47 (55.3)*	43	8.14 [6.14; 18.86] *22 (51.2)*	0.55 [0.32; 0.95] 0.031 AD: + 19.86 weeks
Serious adverse events (SAE)					
	85	73.57 [42.57; n.c.] *29 (34.1)*	43	10.29 [6.14; n.c.] *19 (44.2)*	0.34 [0.18; 0.63] < 0.001 AD: + 63.28 weeks
Therapy discontinuation due to adverse events					
	85	n.a. [n.c.; n.c.] *7 (8.2)*	43	n.a. [n.c.; n.c.] *5 (11.6)*	0.27 [0.07; 1.03] 0.055
Severe AE of CTCAE grade ≥ 3 with an incidence ≥ 5% SOC					
Blood and lymphatic system disorders	85	n.a. [n.c.; n.c.] *9 (10.6)*	43	n.a. [11.71; n.c.] *7 (16.3)*	0.36 [0.13; 1.03] 0.056
Gastrointestinal disorders	85	n.a. [n.c.; n.c.] *17 (20)*	43	n.a. [n.c.; n.c.] *6 (14.0)*	0.74 [0.27; 1.99] 0.548
General disorders and administration site conditions	85	n.a. [n.c.; n.c.] *11 (12.9)*	43	n.a. [10.29; n.c.] *9 (20.9)*	0.28 [0.11; 0.74] 0.010 AD: n.a.

(continuation)

Endpoint	Ripretinib + BSC		Placebo + BSC		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N[g]	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[h] Absolute difference (AD)[b]
Infections and infestations	85	n.a. [n.c.; n.c.] *7 (8.2)*	43	n.a. [19.00; n.c.] *4 (9.3)*	0.23 [0.05; 0.99] 0.049 AD: n.a.
Investigations	85	n.a. [n.c.; n.c.] *13 (15.3)*	43	n.a. [n.c.; n.c.] *4 (9.3)*	0.70 [0.21; 2.38] 0.571
Metabolism and nutrition disorders	85	n.a. [n.c.; n.c.] *11 (12.9)*	43	n.a. [n.c.; n.c.] *4 (9.3)*	0.70 [0.21; 2.35] 0.559
Musculoskeletal and connective tissue disorders	85	n.a. [n.c.; n.c.] *5 (5.9)*	43	n.a. [n.c.; n.c.] *0 (0)*	-[i]
Renal and urinary disorders	85	n.a. [n.c.; n.c.] *2 (2.4)*	43	n.a. [n.c.; n.c.] *3 (7.0)*	0.11 [0.01; 0.97] 0.046 AD: n.a.
Vascular disorders	85	n.a. [n.c.; n.c.] *7 (8.2)*	43	n.a. [n.c.; n.c.] *1 (2.3)*	1.35 [0.15; 11.98] 0.789
Serious AE (SAE) (incidence ≥ 5%) SOC					
Gastrointestinal disorders	85	n.a. [n.c.; n.c.] *12 (14.1)*	43	n.a. [12.57; n.c.] *6 (14.0)*	0.50 [0.17; 1.45] 0.204
General disorders and administration site conditions	85	n.a. [n.c.; n.c.] *5 (5.9)*	43	n.a. [10.29; n.c.] *6 (14.0)*	0.13 [0.04; 0.49] 0.003 AD: n.a.
Infections and infestations	85	n.a. [n.c.; n.c.] *4 (4.7)*	43	n.a. [19.00; n.c.] *4 (9.3)*	0.10 [0.02; 0.60] 0.011 AD: n.a.

Endpoint	Ripretinib + BSC		Placebo + BSC		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N[g]	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[h] Absolute difference (AD)[b]
AEs of special interest of any severity grade (regardless of severity grade) **PT**					
Squamous cell carcinoma	85	n.a. [n.c.; n.c.] *3 (3.5)*	43	n.a. [n.c.; n.c.] *0 (0)*	-[i]
Actinic keratosis	85	n.a. [n.c.; n.c.] *5 (5.9)*	43	n.a. [n.c.; n.c.] *1 (2.3)*	0.49 [0.05; 4.77] 0.538
Keratoacanthoma	85	n.a. [n.c.; n.c.] *0 (0)*	43	n.a. [n.c.; n.c.] *0 (0)*	-[i]
Hyperkeratosis	85	n.a. [n.c.; n.c.] *6 (7.1)*	43	n.a. [n.c.; n.c.] *0 (0)*	-[i]
Melanocytic naevus	85	n.a. [n.c.; n.c.] *6 (7.1)*	43	n.a. [n.c.; n.c.] *0 (0)*	-[i]

[a] Cox proportional hazards model adjusted for number of prior therapies (3 vs ≥ 4) and ECOG-PS (o vs 1 or 2); p value based on two-sided stratified log-rank test
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
[c] from the dossier of the pharmaceutical company (module 4)
[d] defined as 10% deterioration (corresponds to an increase of ≥ 10 points in the score) compared to the start of the study
[e] defined as 15% deterioration (corresponding to a decrease of ≥ 15 points of the scale range) compared to the start of the study.
[f] defined as 10% deterioration (corresponding to a decrease of ≥ 10 points of the scale range) compared to the start of the study.
[g] 1 subject was not included in the safety population in the placebo arm because he/she did not receive a dose of placebo
[h] HR, CI and p value: Cox proportional hazards model, unstratified, calculated post hoc
[i] no adequate estimate

Abbreviations used:
AD = absolute difference; BSC = Best supportive care; 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; SAE = serious adverse event; AE= adverse event; vs = versus

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

Adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib

approx. 220 – 300 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 Qinlock (active ingredient: ripretinib) at the following publicly accessible link (last access: 12 January 2022):

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

Treatment with ripretinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, internal medicine and gastroenterology, and other specialists participating in the Oncology Agreement all of whom are experienced in the treatment of patients with gastrointestinal stromal tumours (GIST).

4. Treatment costs

Annual treatment costs:

Adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ripretinib	€ 302,991.37

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2022)

The annual treatment costs shown refer to the first year of treatment.

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 16 June 2022.

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

Berlin, 16 June 2022

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

Prof. Hecken