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
Avapritinib (new therapeutic indication: systemic mastocytosis, after at least 1 prior therapy)

of 15 September 2022

At its session on 15 September 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. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of avapritinib in accordance with the resolution of 15 April 2021:

Avapritinib

Resolution of: 15 September 2022
Entry into force on: 15 September 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 March 2022):

AYVAKYT is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy.

Therapeutic indication of the resolution (resolution of 15 September 2022):

See new therapeutic indication according to marketing authorisation.

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

Avapritinib is approved as a medicinal product for the treatment of rare diseases under 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 aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy</u>

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.

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

PATHFINDER study (pivotal): ongoing, multicentre, open-label and uncontrolled phase II study; data cut-off from 20 April 2021; safety population

EXPLORER study (supportive): ongoing, multicentre, open-label, uncontrolled phase I study with a phase II expansion; data cut-off from 20 April 2021; safety population

Pooled analyses of the EXPLORER and PATHFINDER studies

Mortality

	Avapritinib	
	N	Median survival time in months [95% CI] *Patients with event n (%)*[a]
EXPLORER	12	n.a. [13; n.a.] 3 (25%)
PATHFINDER	67	n.a. [n.a.; n.a.] 11 (16.4)

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

Morbidity

Endpoint	Avapritinib	
	N	*Patients with event n (%)*[a]
Complete remission (CR) (additional)[h, i]		
EXPLORER	11	1 (9.1)
PATHFINDER	47	1 (2.1)
Pooled	58	2 (3.4)

Endpoint	PATHFINDER study		EXPLORER study		Pooled	
	Avapritinib (N = 67)		Avapritinib (N = 12)		Avapritinib (N = 79)	
	N[a]	MV (SD)	N[a]	MV (SD)	N[a]	MV (SD)
Patient Global Impression of Symptom Severity (PGIS) – Changes from baseline						
Baseline[a, b]	60	2.6 (1.1)	10	2.0 (1.2)	70	2.5 (1.1)
Cycle 1, day 15[a]	52	-0.6 (1.2)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	53	-0.9 (1.2)	9	-0.6 (1.4)	62	-0.8 (1.2)
Cycle 3, day 1[a]	50	-1.0 (1.2)	8[d]	-0.5 (1.2)	58	-1.0 (1.2)
Cycle 4, day 1[a]	-[e]	-[e]	9	-0.6 (1.4)	-[e]	-[e]
EORTC QLQ-C30: Symptom scales – Changes from baseline						
Fatigue						
Baseline[a, b]	60	66.1 (29.0)	10	65.6 (31.2)	70	66.0 (29.1)
Cycle 1, day 15[a]	52	-12.2 (22.6)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	-9.7 (26.0)	9	-25.9 (32.4)	63	-12 (27.3)
Cycle 3, day 1[a]	50	-9.3 (26.2)	8[d]	-26.4 (28.4)	58	-11.7 (26.9)
Cycle 4, day 1[a]	-[e]	-[e]	9	-25.9 (44.8)	-[e]	-[e]
Nausea and vomiting						
Baseline[a, b]	60	15 (26.0)	10	15 (24.2)	70	15 (25.6)
Cycle 1, day 15[a]	52	-1 (22.7)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	-3.7 (27.6)	9	0 (22.0)	63	-3.2 (26.8)
Cycle 3, day 1[a]	50	-4.7 (27.6)	8[d]	4.2 (30.5)	58	-3.4 (27.9)

Cycle 4, day 1[a]	-[e]	-[e]	9	1.8 (22.7)	-[e]	-[e]
Endpoint	**PATHFINDER study**		**EXPLORER study**		**Pooled**	
	Avapritinib (N = 67)		Avapritinib (N = 12)		Avapritinib (N = 79)	
Pain						
Baseline[a, b]	60	40.3 (32.9)	10	41.7 (33.6)	70	40.5 (32.8)
Cycle 1, day 15[a]	52	-14.7 (27.1)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	-13.6 (29.9)	9	-24.1 (31.3)	63	-15.1 (30.0)
Cycle 3, day 1[a]	50	-18.3 (29.8)	8[d]	-10.4 (28.1)	58	-17.2 (29.4)
Cycle 4, day 1[a]	-[e]	-[e]	9	-25.9 (42.6)	-[e]	-[e]
Dyspnoea						
Baseline[a, b]	60	43.9 (36.0)	10	43.3 (35.3)	70	43.8 (35.7)
Cycle 1, day 15[a]	52	-9.6 (32.6)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	-9.9 (34.6)	9	-18.5 (37.7)	63	-11.1 (34.9)
Cycle 3, day 1[a]	50	-14.7 (35.1)	8[d]	-25.0 (34.5)	58	-16.1 (34.9)
Cycle 4, day 1[a]	-[e]	-[e]	9	-25.9 (27.8)	-[e]	-[e]
Insomnia						
Baseline[a, b]	60	55.0 (36.7)	10	46.7 (42.2)	70	53.8 (37.3)
Cycle 1, day 15[a]	52	-14.7 (32.6)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	-19.8 (41.7)	9	-22.2 (52.7)	63	-20.1 (43.0)
Cycle 3, day 1[a]	50	-17.3 (39.4)	8[d]	-8.3 (58.4)	58	-16.1 (42.0)
Cycle 4, day 1[a]	-[e]	-[e]	9	-18.5 (50.3)	-[e]	-[e]
Loss of appetite						
Baseline[a, b]	60	41.1 (33.8)	10	36.7 (39.9)	70	40.5 (34.5)
Cycle 1, day 15[a]	52	-16.0 (31.3)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	-18.5 (38.1)	9	-3.7 (51.2)	63	-16.4 (40.1)
Cycle 3, day 1[a]	50	-22.0 (42.9)	8[d]	-4.2 (62.8)	58	-19.5 (45.9)
Cycle 4, day 1[a]	-[e]	-[e]	9	-3.7 (53.9)	-[e]	-[e]
Constipation						
Baseline[a, b]	60	21.1 (31.3)	10	16.7 (28.3)	70	20.5 (30.7)
Cycle 1, day 15[a]	52	-1.3 (24.7)	-[c]	-[c]	-[c]	-[c]

Cycle 2, day 1[a]	54	-8.6 (29.1)	9	-11.1 (33.3)	63	-9 (29.5)
Endpoint	**PATHFINDER study**		**EXPLORER study**		**Pooled**	
	Avapritinib (N = 67)		Avapritinib (N = 12)		Avapritinib (N = 79)	
Cycle 3, day 1[a]	50	-4.7 (32.3)	8[d]	-12.5 (35.4)	58	-5.8 (32.5)
Cycle 4, day 1[a]	-[e]	-[e]	9	-14.8 (29.4)	-[e]	-[e]
Diarrhoea						
Baseline[a, b]	60	34.4 (37.8)	10	50.0 (45.1)	70	36.7 (39.0)
Cycle 1, day 15[a]	52	-13.5 (39.7)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	-11.1 (39.4)	9	-7.4 (49.4)	63	-10.6 (40.5)
Cycle 3, day 1[a]	50	-17.3 (40.5)	8[d]	-4.2 (51.8)	58	-15.5 (42.0)
Cycle 4, day 1[a]	-[e]	-[e]	9	-18.5 (55.6)	-[e]	-[e]

Health-related quality of life

Endpoint	**PATHFINDER study**		**EXPLORER study**		**Pooled**	
	Avapritinib (safety population) (N = 67)		Avapritinib (safety population) (N = 12)		Avapritinib (safety population) (N = 79)	
EORTC QLQ-C30: Functional scales and general health scale – Changes from baseline						
General health status						
Baseline[a, b]	60	38.2 (24.3)	10	44.2 (26.9)	70	39.0 (24.6)
Cycle 1, day 15[a]	52	13.1 (22.3)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	13.6 (24.9)	9	25.0 (31.2)	63	15.2 (25.9)
Cycle 3, day 1[a]	50	16.8 (28.4)	8[d]	25.0 (31.5)	58	18.0 (28.7)
Cycle 4, day 1[a]	-[e]	-[e]	9	24.1 (40.1)	-[e]	-[e]
Physical functioning						
Baseline[a, b]	60	55.4 (26.9)	10	60.0 (28.3)	70	56.1 (27.0)
Cycle 1, day 15[a]	52	8.8 (15.6)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	6.8 (19.7)	9	16.3 (23.1)	63	8.2 (20.3)
Cycle 3, day 1[a]	50	7.7 (21.0)	8[d]	17.5 (15.5)	58	9.1 (20.5)
Cycle 4, day 1[a]	-[e]	-[e]	9	20 (22.4)	-[e]	-[e]

Endpoint	PATHFINDER study		EXPLORER study		Pooled	
	Avapritinib (safety population) (N = 67)		Avapritinib (safety population) (N = 12)		Avapritinib (safety population) (N = 79)	
Role functioning						
Baseline[a, b]	60	45.6 (32.9)	10	45.0 (29.4)	70	45.5 (32.2)
Cycle 1, day 15[a]	52	7.4 (21.0)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	8.3 (29.3)	9	31.5 (28.2)	63	11.6 (30.0)
Cycle 3, day 1[a]	50	11 (28.7)	8[d]	20.8 (31.8)	58	12.4 (29.0)
Cycle 4, day 1[a]	-[e]	-[e]	9	25.9 (47.2)	-[e]	-[e]
Emotional functioning						
Baseline[a, b]	60	61.5 (27.2)	10	71.7 (25.2)	70	63.0 (27.0)
Cycle 1, day 15[a]	52	5.6 (20.1)	-	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	7.4 (23.9)	9	8.3 (26.7)	63	7.5 (24.1)
Cycle 3, day 1[a]	50	7.7 (21.7)	8[d]	14.9 (20.5)	58	8.7 (21.6)
Cycle 4, day 1[a]	-[e]	-[e]	9	14.8 (22.0)	-[e]	-[e]
Cognitive functioning						
Baseline[a, b]	60	73.3 (25.7)	10	73.3 (16.1)	70	73.3 (24.5)
Cycle 1, day 15[a]	52	1.3 (13.9)	-[c]	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	-0.9 (19.5)	9	13 (23.2)	63	1.1 (20.5)
Cycle 3, day 1[a]	50	0.3 (19.8)	8[d]	14.6 (18.8)	58	2.3 (20.1)
Cycle 4, day 1[a]	-[e]	-[e]	9	11.1 (20.4)	-[e]	-[e]
Social functioning						
Baseline[a, b]	60	51.7 (31.5)	10	56.7 (32.6)	70	52.4 (31.5)
Cycle 1, day 15[a]	52	12.5 (27.2)	-	-[c]	-[c]	-[c]
Cycle 2, day 1[a]	54	13.3 (30.8)	9	22.2 (36.3)	63	14.6 (31.5)
Cycle 3, day 1[a]	50	10.3 (24.9)	8[d]	20.8 (26.4)	58	11.8 (25.2)
Cycle 4, day 1[a]	-[e]	-[e]	9	18.5 (28.2)	-[e]	-[e]

Side effects

Endpoint	PATHFINDER study		EXPLORER study		Pooled[f]	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]
Adverse events in total						
	67	67 (100)	12	12 (100)	79	79 (100)
Serious adverse events (SAEs)[g]						
	67	27 (40.3)	12	5 (41.7)	79	32 (40.5)
Severe adverse events (CTCAE grade 3 or 4)[g]						
	67	48 (71.6)	12	9 (75.0)	79	57 (72.2)
Therapy discontinuation due to adverse events[g]						
	67	12 (17.9)	12	0 (0)	79	12 (15.2)
AESI category Preferred term	**PATHFINDER study**		**EXPLORER study**		**Pooled**	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]
Adverse events of special interest						
Subjects with at least one AESI regardless of severity grade						
Cognitive effects	67	13 (19.4)	12	3 (25.0)	79	16 (20.3)
Cognitive disorder	67	8 (11.9)	12	2 (16.7)	79	10 (12.7)
Impaired memory	67	3 (4.5)	12	1 (8.3)	79	4 (5.1)
State of confusion	67	1 (1.5)	12	0 (0)	79	1 (1.3)
Intracranial haemorrhage	67	1 (1.5)	12	1 (8.3)	79	2 (2.5)
Subdural haematoma	67	1 (1.5)	12	1 (8.3)	79	2 (2.5)
Subjects with ≥ 1 severe AESI ≥ grade 3[f,g]						
Cognitive effects	67	3 (4.5)	12	0 (0)	79	3 (3.8)
Cognitive disorder	67	2 (3.0)	12	0 (0)	79	2 (2.5)
Intracranial haemorrhage	67	1 (1.5)	12	0 (0)	79	1 (1.3)
Subdural haematoma	67	1 (1.5)	12	0 (0)	79	1 (1.3)
AESI category	**PATHFINDER study**		**EXPLORER study**		**Pooled**	

Preferred term	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]
Subjects with ≥ 1 serious AESI[f,g]						
Intracranial haemorrhage	67	1 (1.5)	12	1 (8.3)	79	2 (2.5)
Subdural haematoma	67	1 (1.5)	12	1 (8.3)	79	2 (2.5)

[a] Subjects with available values
[b] Baseline is defined as the first treatment day (C1D1) in both the PATHFINDER and EXPLORER studies.
[c] In the EXPLORER study, no assessment takes place at this time.
[d] A single subject is already enrolled in the EXPLORER study proportionally at 8.3%. Falling short of the return rate of 70% for this individual cycle is low at 3.3%. Therefore, the results for cycle 3 are presented in the EXPLORER study.
[e] There is no assessment in the PATHFINDER study at this time.
[f] When interpreting the pooled results, it must be taken into account that the severity grading in the PATHFINDER study is made according to CTCAE version 5.0 and in the EXPLORER study according to version 4.03, so that for some AEs differences in gradations may exist between the two studies.
[g] Missing severity grade information and/or causality information is not imputed, but is classified as "missing" .
[h] Evaluations for the endpoint "CR" based on the "population with evaluable response according to Study Steering Committee" (SSC-RE in PATHFINDER) and the "population with evaluable response according to the "Adjustment Commission" (RAC-RE in EXPLORER)
i The primary endpoint of the PATHFINDER study is the adjusted overall response rate (adjORR). In the Explorer study, ORR was defined as a secondary endpoint. The change in the IWG criteria to mIWG criteria was based on preliminary data from the EXPLORER study and was accompanied by inclusion of CRh (complete remission with partial increase in peripheral blood count) as a component of ORR.
The inclusion of CRh, based on preliminary data from the EXPLORER study as a component of the endpoint ORR, is viewed critically, as this primarily assumes an outcome-driven inclusion in the operationalisation of the criteria. Therefore, complete remission (CR) is presented as an alternative to the primary endpoint ORR.

Abbreviations used:
AESI: adverse events of special interest; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.e. = not evaluable; SD = standard deviation; (S)AE = (Serious) Adverse Event

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

Adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy

approx. 270 to 680 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 Ayvakyt (active ingredient: avapritinib) at the following publicly accessible link (last access: 1 July 2022):

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

Treatment with avapritinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with mastocytosis.

This medicinal product was authorised under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

Avapritinib has been associated with an increased incidence of haemorrhagic events. The risk of intracranial haemorrhage should be carefully assessed before the start of treatment.

4. Treatment costs

Annual treatment costs:
Adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Avapritinib	€ 257,970.81

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2022)

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 15 September 2022.

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

Berlin, 15 September 2022

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

Prof. Hecken