Gemeinsamer Bundesausschuss

Avapritinib

Resolution of: 15 April 2021 valid until: unlimited
Entry into force on: 15 April 2021
BAnz AT 25.05.2021 B3

Therapeutic indication (according to the marketing authorisation of 24 September 2020):

Ayvakyt is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

Therapeutic indication of the resolution (resolution from the 15 April 2021):

see therapeutic indication according to marketing authorisation

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

Avapritinib 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 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 Ordinance on the Benefit Assessment of Pharmaceuticals (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 unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation

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

Hint of a non-quantifiable additional benefit, because the scientific data does not allow a quantification.

Study results according to endpoints:[1]

Adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation

Summary of results for relevant clinical endpoints

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

NAVIGATOR study (BLU-285-1101)

Study design: non-controlled, multicentre, international, phase I/II

Data cut-off: 9 March 2020 (unless otherwise specified)

Mortality[a]

Endpoint	NAVIGATOR	
	N	Median survival time in months [95%-CI][b, c] *Patients with event n (%)*
Overall survival		
Data cut-off 9 March 2020	28	n. a. [n. c.; n. c.] *8 (28.6)*
Data cut-off 29 January 2021 (presented additionally)	28	n. a. [37.3; n. c.] *9 (32.1)*

Endpoint	NAVIGATOR	
	N	Kaplan-Meier estimation [95 %-CI][b, c]
Overall survival		
To study month 30 (presented additionally)	28	69.7 [52.1; 87.3]

(continuation)

[1] Data from the dossier assessment of the G-BA (published on the 1 February 2021) the amendment to, unless otherwise indicated.

Morbidity[a, d]

Endpoint	NAVIGATOR	
	N	Median survival time in months [95%-CI][e] *Patients with event n (%)*
Progression-free survival (PFS)		
	28	24.0 [16.8; n. a.] *15 (53.6)*

Endpoint	NAVIGATOR	
	N	Response rate in % [95%-CI][f] *Patients with event n (%)*
Overall response rate (presented additionally)		
Overall Response Rate (complete response/ Partial response)	28	96.4 [81.7; 99.9] *27 (96.4)*
Complete response	28	10.7 [2.3; 28.2] *3 (10.7)*
Partial response	28	85.7 [67.3; 96.0] *24 (85.7)*

Health-related quality of life

No data available.

Side effects[a]

Endpoint PT	NAVIGATOR	
	N	Patients with event n (%)
Total adverse events (presented additionally)		
	28	28 (100.0)
Serious adverse events (SAE)		
	28	21 (75.0)
Severe adverse events (CTCAE grade ≥ 3)		
	28	27 (96.4)
Therapy discontinuation because of adverse events		
	28	10 (35.7)

(continuation)

Adverse Events of special interest		
Cognitive effects	28	19 (67.9)
Cognitive disorders	28	14 (50.0)
Memory impairment	28	6 (21.4)
State of confusion	28	5 (17.9)
Encephalopathy	28	0
Intracranial haemorrhages	28	2 (7.1)
Intracranial haemorrhages	28	2 (7.1)
Brain haemorrhage	28	0
Subdural haematoma	28	0

Endpoint	**NAVIGATOR**	
SOC **PT**	N	Patients with event n (%)
SAE according to SOC/PT with incidence ≥ 5%		
Gastrointestinal disorders	28	7 (25.0)
Infections and infestations	28	7 (25.0)
Upper respiratory tract infection	28	2 (7.1)
Urinary tract infection	28	2 (7.1)
Nervous system disorders	28	4 (14.3)
Intracranial haemorrhages	28	2 (7.1)
Blood and lymphatic system disorders	28	4 (14.3)
Anaemia	28	4 (14.3)
General disorders and administration site conditions	28	4 (14.3)
Disease progression	28	2 (7.1)
Psychiatric disorders	28	2 (7.1)

(continuation)

Respiratory, thoracic and mediastinal disorders	28	3 (10.7)
Injury, poisoning, and procedural complications	28	2 (7.1)
Skin and subcutaneous tissue disorders	28	2 (7.1)
Severe AE (CTCAE-Grade ≥ 3) after SOC/PT with incidence ≥ 5%		
Blood and lymphatic system disorders	28	16 (57.1)
Anaemia	28	13 (46.4)
Neutropenia	28	3 (10.7)
Metabolism and nutrition disorders	28	10 (35.7)
Hypokalemia	28	4 (14.3)
Hypophosphataemia	28	2 (7.1)
Hyponatremia	28	2 (7.1)
Gastrointestinal disorders	28	8 (28.6)
Diarrhoea	28	3 (10.7)
Investigations, examinations	28	11 (39.3)
Neutrophil count	28	5 (17.9)
Infections and infestations	28	4 (14.3)
Respiratory, thoracic and mediastinal disorders	28	4 (14.3)
Pleural effusion	28	2 (7.1)
General disorders and administration site conditions	28	4 (14.3)
Disease progression	28	2 (7.1)
Nervous system disorders	28	4 (14.3)
Intracranial haemorrhages	28	2 (7.1)
Psychiatric disorders	28	2 (7.1)

(continuation)

Injury, poisoning, and procedural complications	28	2 (7.1)

[a] Safety population; the safety population refers to all patients who have received at least one dose of avapritinib. Only patients with a PDGFRA-D842V mutation who were treated with the product information-compliant starting dose of 300 mg/day are included.
[b] Kaplan-Meier estimates with censoring at the data cut-off point or at the last date + 1 day on which vital status was recorded as "alive", depending on which censoring reason occurred earlier.
[c] Confidence intervals calculated using linear transformation
[d] Data from the dossier Avapritinib Modul 4A of 12 October 2020
[e] Estimation using the Kaplan-Meier method. Confidence intervals calculated using linear transformation.
[f] Two-sided 95% CI based on the exact binomial distribution using the Clopper-Pearson method.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; CI = Confidence Interval; N = Number of patients evaluated; n = Number of patients with (at least one) event; n. a. = not assesable n. c. = not calculable; PT = Preferred Term; SOC = System Organ Class

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

Adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation

approx. 1 to 90 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: 24 March 2021):

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

Treatment with avapritinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gastroenterology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with gastrointestinal stromal tumours.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will assess new information on this medicinal product at least annually and update the product information for healthcare professionals as necessary.

Patient selection for treatment of gastrointestinal stromal tumours with the PDGFRA-D842V mutation should be based on a validated testing method.

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

4. Treatment costs

Annual treatment costs:

Adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation

Designation of the therapy	Annual treatment costs/patient
Avapritinib	€ 409,150.28

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 March 2021).

Costs for additionally required SHI services: not applicable