Avapritinib (new therapeutic indication: indolent systemic mastocytosis (ISM))

Resolution of: 20 June 2024 valid until: unlimited

Entry into force on: 20 June 2024

Federal Gazette, BAnz AT 31.07.2024 B2

New therapeutic indication (according to the marketing authorisation of 11 December 2023):

AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.

Therapeutic indication of the resolution (resolution of 20 June 2024):

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).

Adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment

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

Indication of a minor additional benefit

Study results according to endpoints:[1]

Adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment

[1] Data from the dossier assessment of the G-BA (published on 2. April 2024), and from the amendment tothe dossier assessment from 28 May 2024, unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑↑	Advantage in the endpoints of ISM-SAF (skin domain and most severe leading domain/ -symptom cluster), PGIS and EQ-5D VAS
Health-related quality of life	↑	Advantage in the PCS of the SF-12
Side effects	↔	No relevant difference for the benefit assessment; in detail, disadvantage in the endpoint of oedema (AE of special interest)

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
∅: No data available.
n.a.: not assessable

PIONEER study, part 2

- Multi-centre phase II study with double-blind, randomised, controlled study phase (part 2; 24 weeks)
- Avapritinib + best supportive care vs placebo + best supportive care
- Population: Patients with confirmed systemic mastocytosis and moderate to severe symptoms based on a mean ISM-SAF TSS ≥ 28 despite symptomatic therapy in the screening phase.

Mortality

Endpoint	Avapritinib + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Overall survival					
No deaths occurred.					

Morbidity

Endpoint Study	Avapritinib + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[b]
ISM-SAF - percentage of subjects with an improvement of at least 15% of the scale range at week 24					
Total symptom score (≥ 16.5 points)	141	54 (38.3)	71	19 (26.8)	1.47 [0.94; 2.27] 0.09
Gastrointestinal symptom score (≥ 4.5 points)	141	45 (31.9)	71	25 (35.2)	0.94 [0.64; 1.38] > 0.999
Skin symptom score (≥ 4.5 points)	141	70 (51.1)	71	19 (26.8)	1.94 [1.27; 2.96] 0.002
Neurocognitive symptom cluster (≥ 4.5 points)	141	49 (34.8)	71	20 (28.2)	1.26 [0.82; 1.93] 0.29
PGIS - percentage of subjects with an improvement of at least 15% of the scale range at week 24 (≥ 1 point)					
	141	72 (51.1)	71	24 (33.8)	1.54 [1.07; 2.21] 0.020
PGIC - percentage of subjects with an improvement of at least 15% of the scale range at week 24 (≥ 1.5 points)					
	141	11 (7.8)	71	1 (1.4)	5.81 [0.64; 53.03] 0.12
EQ-5D VAS - percentage of subjects with an improvement of at least 15 % of the scale range at week 24 (≥ 15 points)					
	141	40 (28.4)	71	4 (9.9)	2.88 [1.36; 6.12] 0.006

Endpoint	Avapritinib + BSC				Placebo + BSC				Intervention vs control
	Values Start of study		Change at week 24		Values Start of study		Change at week 24		Mean difference [95% CI] p value[c]
	N	MV (SD)	N	MV (SD)	N	MV (SD)	N	MV (SD)	Hedges' g [95% CI]
Symptoms using ISM-SAF									
(most severe) lead symptom[d]	139	7.66 (1.69)	131	-2.19 (0.22)	71	7.91 (1.68)	66	-1.38 (0.29)	-0.81 [-1.46; -0.17] 0.014 -0.32 [-0.63; -0.03]
(most severe) lead domain/ symptom cluster[e]	139	17.51 (6.03)	131	-6.18 (0.57)	71	18.58 (6.40)	66	-2.90 (0.75)	-3.16 [-4.69; -1.63] < 0.0001 -0.51 [-0.82; -0.21]

Health-related quality of life

Endpoint	Avapritinib + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[b]
Health-related quality of life using SF-12 - percentage of subjects with an improvement of at least 15% of the scale range at week 24					
PCS (≥ 9.1 points)	141	71 (50.4)	71	25 (35.2)	1.43 [1.01; 2.03] 0.042
MCS (≥ 8.5 points)	141	70 (49.6)	71	30 (42.3)	1.19 [0.87; 1.63] 0.29

Endpoint	Avapritinib + BSC				Placebo + BSC				Intervention vs control
	Values Start of study		Change at week 24		Values Start of study		Change at week 24		Mean difference [95% CI] p value[c]
	N	MV [SD]	N	LS mean (SE)	N	MV (SD)	N	LS mean (SE)	Hedges' g [95% CI]
Disease-specific quality of life using MC-QoL									
Total score[f]	135	57.50 (16.02)	121	-16.73 (1.86)	68	57.47 (17.20)	60	-6.93 (2.46)	-9.80 [-15.09; -4.51] < 0.001 -0.49 [-0.81; -0.18]
Symptoms[f]	135	65.14 (16.07)	121	-16.28 (2.01)	68	63.93 (17.55)	60	-7.58 (2.67)	-8.70 [-14.44; -2.97] 0.003 -0.40 [-0.72; -0.09]
Social life/ functioning[f]	135	55.84 (21.02)	121	-17.14 (2.20)	68	55.33 (22.82)	60	-5.84 (2.91)	-11.30 [-17.57; -5.03] < 0.001 -0.48 [-0.80; -0.17]
Emotions[f]	135	49.51 (23.39)	121	-17.04 (2.22)	68	48.98 (22.86)	60	-8.07 (2.94)	-8.97 [-15.29; -2.65] 0.006 -0.37 [-0.69; -0.06]
Skin[f]	135	55.49 (22.33)	121	-16.12 (2.54)	68	61.89 (22.69)	60	-6.28 (3.37)	-9.84 [-17.09; -2.59] 0.008 0.36 [-0.68; -0.05]

Side effects

Endpoint	Avapritinib + BSC		Placebo + BSC		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)	141	128 (90.8)	71	66 (93.0)	-
Serious adverse events (SAE)	141	7 (5.0)	71	8 (11.3)	1.01 [0.58; 1.75] 0.98

Severe adverse events (CTCAE grade 3 or 4)	141	30 (21.3)	71	15 (21.1)	0.44 [0.17; 1.17] 0.10
Therapy discontinuation due to adverse events	141	3 (2.1)	71	1 (1.4)	1.51 [0.16; 14.26] 0.72
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No suitable data available					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No suitable data available					
Adverse events of special interest (with statistically significant difference between the treatment arms)					
Oedema	141	36 (25.5)	71	8 (11.3)	2.27 [1.11; 4.61] 0.024 AD = 14.2%

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. Two-tailed p value of RR based on the asymptotic normal approximation of the logarithmised Mantel-Haenszel estimate, stratified by stratification factor (serum tryptase < 20 ng/ml vs ≥ 20 ng/ml) and baseline ISM status (moderate vs severe).
c. ANCOVA model controlled for stratification factor (serum tryptase) and baseline ISM status (moderate vs severe), one-tailed p value.
d. Scale from 0 to 10. The higher the score, the more pronounced the symptoms.
e. Scale from 0 to 30. The higher the score, the more pronounced the symptoms.
f. Values between 0 (low impairment of quality of life) and 100 (high impairment of quality of life).

Abbreviations used:
AD = Absolute Difference; ANCOVA = Analysis of Covariance; BSC = Best Supportive Care; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D VAS = Visual Analogue Scale of the European Quality of Life 5-Dimension; ISM = Indolent Systemic Mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis Symptom Assessment Form; CI = confidence interval; LS = least squares; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PGIS = Patient Global Impression of Severity; RR = relative risk; SF-12 = Short Form 12 Health Survey; SOC = system organ class; SAE = serious adverse event; SD = standard deviation; SE = standard error; AE = adverse event; vs = versus

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

<u>Adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment</u>

Approx. 715 – 1,000 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: 4 April 2024):

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 experienced in the treatment of indolent systemic mastocytosis.

This medicinal product received a conditional marketing authorisation. 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.

4. Treatment costs

Annual treatment

costs:

Adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Avapritinib	€ 193,497.69

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2024)

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment

– No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.