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
Avacopan (granulomatosis with polyangiitis or microscopic polyangiitis, combination with rituximab or cyclophosphamide)

of 4 August 2022

At its session on 4 August 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive 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 Avacopan as follows:**

Avacopan

Resolution of: 4 August 2022
Entry into force on: 4 August 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 19 January 2022):

Tavneos, in combination with a rituximab or cyclophosphamide dosing scheme, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

Therapeutic indication of the resolution (resolution of 4 August 2022):

See therapeutic indication according to marketing authorisation.

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

Avacopan 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 severe active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)

Extent of the additional benefit and significance of the evidence of Avacopan in combination with a rituximab or cyclophosphamide dosing scheme:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults with severe active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)

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 endpoint "sustained remission".
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment. In detail, advantage for the AE of SOC "Eye disorders", "Benign, malignant and non-specific neoplasms (including cysts and polyps)" and "Endocrine disorders".
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		

ADVOCATE study: Randomised controlled trial over 52 weeks, avacopan vs prednisone, each in combination with a cyclophosphamide (followed by azathioprine/ mycophenolate mofetil) or rituximab (without maintenance treatment) dosing scheme

Mortality

Endpoint	Avacopan N = 166	Prednisone N = 164
	Deaths n (%)	Deaths n (%)
Overall mortality	2 (1)	4 (2)

[1] Data from the dossier assessment of the G-BA (published on 16. Mai 2022), unless otherwise indicated.

Morbidity

Endpoint	Avacopan N = 166	Prednisone N = 164	Avacopan vs prednisone
	Patients with event n (%)	Patients with event n (%)	Relative risk [95% CI][a]; p value[b]
Remission			
Remission (in week 26)	120 (72)	115 (70)	1.03[a] [0.90; 1.18] 0.239
Sustained remission (in week 52)	109 (66)	90 (55)	1.20[a] [1.002; 1.43] 0.007

Endpoint	Avacopan N = 166			Prednisone N = 164			Avacopan vs Prednisone
	n	Values at baseline MV (SD)	Change at week 26/56 LS-MV (SE)[c]	n	Values at baseline MV (SD)	Change at week 26/56 LS-MV (SE)[c]	LS-MD [95% CI]; p value[d]
Health status (EQ-5D VAS)[e]							
Change at week 26	150	65.8 (19.5)	9.1 (1.4)	153	63.4 (22.7)	5.5 (1.4)	3.6 [-0.1; 7.2]; 0.053
Change at week 52	149		13.0 (1.4)	146		7.1 (1.4)	5.9 [2.3; 9.6]; 0.002 Hedges' g 0.37 [0.14; 0.60]

Health-related quality of life

Endpoint	Avacopan N = 166			Prednisone N = 164			Avacopan vs Prednisone
	N[f]	Values at baseline MV (SD)	Change at week 26/56 LS-MV[c] (SE)	N[f]	Values at baseline MV (SD)	Change at week 26/56 LS-MV[c] (SE)	LS-MD [95% CI][d]; p value
SF-36[e]							
Mental component score (MCS)							
Change at week 26	154	44.2 (12.7)	4.8 (0.8)	147	42.1 (13.3)	3.3 (0.8)	1.6 [-0.6; 3.8]; 0.158
Change at week 52	148		6.4 (0.8)	144		4.7 (0.8)	1.7 [-0.5; 3.9]; 0.133
Physical component score (PCS)							
Change at week 26	153	39.2 (10.3)	4.4 (0.7)	147	40.1 (10.5)	1.3 (0.7)	3.1 [1.2; 5.0]; 0.002 Hedges' g 0.36 [0.14; 0.59]
Change at week 52	147		5.0 (0.7)	144		2.6 (0.8)	2.4 [0.4; 4.3]; 0.018 Hedges' g 0.28 [0.05; 0.51]

Side effects

Endpoints	Avacopan N = 166	Prednisone N = 164	Avacopan vs Prednisone
	Patients with event n (%)	Patients with event n (%)	Relative risk [95% CI]; p value[g]
Summary of the AEs			
AE	164 (99)	161 (98)	
AE grade ≥ 3	49 (30)	59 (36)	n.d.
SAE	70 (42)	74 (45)	0.93 [0.73; 1.19]; 0.667
AEs which led to the discontinuation of the study medication	27 (16)	28 (17)	0.95 [0.59; 1.54]; 0.961
AE by system organ class (occurred in ≥ 10% of patients in at least one study arm)			
Infections and infestations	113 (68)	124 (76)	0.90 [0.79; 1.03]; 0.167
Gastrointestinal disorders	101 (61)	83 (51)	1.20 [0.99; 1.46]; 0.078
Musculoskeletal and connective tissue disorders	92 (55)	93 (57)	0.98 [0.81; 1.18]; 0.901

General disorders and administration site conditions	76 (46)	87 (53)	0.86 [0.69; 1.07]; 0.226
Skin and subcutaneous tissue disorders	73 (44)	85 (52)	0.85 [0.69; 1.06]; 0.188
Nervous system disorders	71 (43)	73 (45)	0.96 [0.75; 1.23]; 0.835
Investigations	69 (42)	67 (41)	1.02 [0.73; 1.31]; 0.984
Respiratory, thoracic and mediastinal disorders	68 (41)	80 (49)	0.84 [0.66; 1.07]; 0.188
Metabolism and nutrition disorders	55 (33)	62 (38)	0.88 [0.66; 1.17]; 0.440
Vascular disorders	48 (29)	48 (29)	0.99 [0.71; 1.38]; 1.000
Blood and lymphatic system disorders	45 (27)	54 (33)	0.82 [0.59; 1.15]; 0.302
Injury, poisoning and procedural complications	37 (22)	48 (29)	0.76 [0.53; 1.10]; 0.186
Psychiatric disorders	32 (19)	44 (27)	0.72 [0.48; 1.07]; 0.134
Immune system disorders	30 (18)	41 (25)	0.72 [0.48; 1.10]; 0.162
Renal and urinary disorders	27 (16)	28 (17)	0.95 [0.59; 1.54]; 0.961
Cardiac disorders	26 (16)	21 (13)	1.22 [0.72; 2.06]; 0.558
Eye disorders	25 (15)	43 (26)	0.58 [0.37; 0.90]; 0.018
Ear and labyrinth disorders	20 (12)	16 (10)	1.23 [0.67; 2.26]; 0.623
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6 (4)	16 (10)	0.39 [0.16; 0.94]; 0.044
Endocrine disorders	5 (3)	22 (13)	0.24 [0.10; 0.60]; 0.001
SAEs by system organ class (occurred in ≥ 5% of patients in at least one study arm)			
Infections and infestations	22 (13)	25 (15)	0.87 [0.52; 1.47]; 0.719
Immune system disorders	14 (8)	21 (13)	0.67 [0.36; 1.25]; 0.267
Gastrointestinal disorders	8 (5)	11 (7)	0.73 [0.31; 1.73]; 0.617
Respiratory, thoracic and mediastinal disorders	7 (4)	12 (7)	0.60 [0.25; 1.43]; 0.331
General disorders and administration site conditions	4 (2)	9 (6)	0.47 [0.16; 1.41]; 0.248
Blood and lymphatic system disorders	3 (2)	11 (7)	0.30 [0.09; 0.98]; 0.053
AEs of interest			
Infection			
AEs total	113 (68)	124 (76)	
Severe AEs (grade ≥ 3)	14 (8)	14 (9)	

SAE	22 (13)	25 (15)	
Hypersensitivity			
AEs total	68 (41)	70 (43)	
Elevated values in liver function tests			
AEs total	22 (13)	19 (12)	
Decreased leukocyte count			
AEs total	31 (19)	39 (24)	

a. RR and 95% CI (Wald method): Evaluated without stratification.
b. 1-sided p value at the α-level of 0.025 significant: adjusted according to the stratification factors.
c. Mean change between the respective measurement time point and baseline per treatment group.
d. Difference in mean change between the respective measurement time point and baseline between the treatment groups, positive effects (intervention minus control) mean an advantage for the intervention.
e. Higher values mean better health status (EQ5D-VAS), better quality of life (SF-36) or better renal function (eGFR).
f. Renal involvement was operationalised as the presence of ≥ 1 kidney-related item in the BVAS.
g. RR, 95% CI and two-sided p-value: Non-stratified.

Abbreviations:
eGFR: estimated glomular filtration rate; EQ-5D-VAS: Visual Analogue Scale of the European Quality of Life – 5 Dimensions; n.d.: no data available; CI: confidence interval; LS: Least Squares; MD: mean difference; MV: mean value; N = number of patients evaluated; n = number of patients with (at least one) event; RR: relative Risk; SD: standard deviation; SE: standard error; SF-36: Short Form-36 Health Survey; (S)AE: (serious) adverse event; vs = versus

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

Adults with severe active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)

approx. 2,180 – 2,280 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 Tavneos (active ingredient: avacopan) at the following publicly accessible link (last access: 04 May 2022):

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

Treatment with avacopan should only be initiated and monitored by doctors experienced in treating GPA or MPA.

Avacopan has not been investigated in patients with severe disease, manifesting as alveolar haemorrhage requiring invasive ventilation and in patients with an estimated glomerular filtration rate (eGFR) below 15 ml/min/1,73m^2 who are subject to mandatory dialysis requirement or are in need of dialysis or plasma exchange treatment.

In order to further characterise the safety profile of avacopan with respect to e.g., liver injury, severe infections, malignancies and cardiovascular events, a PASS study was requested by the EMA upon marketing authorisation.

4. Treatment costs

Annual treatment costs:

Adults with severe active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Avacopan in combination with a rituximab or cyclophosphamide dosing scheme	
Avacopan in combination with rituximab and glucocorticoids, if necessary[2]	
Avacopan	€ 49,456.95
Rituximab	€ 10,856.86
Prednisolone	Different from patient to patient
Avacopan + rituximab	€ 60,313.81 - € 92,884.39
Avacopan + rituximab + prednisolone	Different from patient to patient
Additionally required SHI costs	€ 101.03
Avacopan in combination with cyclophosphamide (intravenous, IV)[3] *and glucocorticoids, if necessary*	
Avacopan	€ 49,456.95
Cyclophosphamide IV	€ 177.68 - € 294.00
Prednisolone	Different from patient to patient
Avacopan + cyclophosphamide IV	€ 49,634.63 - € 49,750.95
Avacopan + cyclophosphamide IV + prednisolone	Different from patient to patient
Avacopan in combination with cyclophosphamide (peroral, PO)[3] *and glucocorticoids, if necessary*	
Avacopan	€ 49,456.95
Cyclophosphamide PO	143.94
Prednisolone	Different from patient to patient
Avacopan + cyclophosphamide PO	€ 49,600.89
Avacopan + cyclophosphamide PO + prednisolone	Different from patient to patient

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

[2] Prednisolone from the group of glucocorticoids was presented as an example.
[3] Following treatment with cyclophosphamide, azathioprine or, if necessary, mycophenolate mofetil should be used in combination with avacopan according to the product information (Tavneos, last revised: 01/2022). These are not taken into account for the calculation of the annual treatment costs as they are not approved for the therapeutic indication to be assessed.

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Num-ber/ cycle	Number/ patient/ year	Costs/ patient/ year
Cyclophosphamide IV	Surcharge for production of a parenteral prepara-tion containing cytostatic agents	€ 81	1	4.3 – 6.5[4]	€ 348.30 - € 526.50
Rituximab	Surcharge for the prepa-ration of a parenteral so-lution containing mono-clonal antibodies	€ 71	4	4	€ 284

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 4 August 2022.

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

Berlin, 4 August 2022

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

Prof. Hecken

[4] A maximum duration of 13 weeks = 91 days is used.