Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient avacopan in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 February 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 11 February 2022.

Avacopan indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis or microscopic polyangiitis 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.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 16 May 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of avacopan.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Avacopan (Tavneos) in accordance with the product information

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 the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of avacopan in combination with a rituximab or cyclophosphamide dosing scheme is assessed as follows:

For adults with severe active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), there is a hint for a minor additional benefit for avacopan in combination with a rituximab or cyclophosphamide dosing scheme.

Justification:

The phase III ADVOCATE (CL010_168) study is used for the present benefit assessment procedure according to Section 35a SGB V.

In addition, the pharmaceutical company submitted the CLEAR (CL002_168) study. This is a randomised, double-blind, placebo-controlled, 3-stage, phase II study with a treatment duration of 12 weeks to investigate the safety and efficacy of avacopan in adults with GPA, MPA or renal limited vasculitis. With a significantly shorter treatment duration, the CLEAR study does not provide any relevant information on the benefit assessment beyond that of the 52-week ADVOCATE study. In addition, an adjustment of the glucocorticoid therapy in the study - contrary to the requirements in the product information to use glucocorticoids as clinically indicated - resulted in the discontinuation of the study medication. Overall, the CLEAR study is therefore not used for the present benefit assessment.

The ADVOCATE study is a double-blind, multicentre randomised controlled trial comparing the efficacy and safety of avacopan versus prednisone, each in combination with background therapy. 328 adults and 3 adolescents with severe active GPA or MPA requiring treatment with cyclophosphamide (CYC) or rituximab (RTX) were enrolled in the study. The majority of the study participants were newly diagnosed with the disease. 31% of the study participants had relapsed GPA or MPA. At least one of the following criteria related to the Birmingham Vasculitis Activity Score (BVAS) had to be met at the time of enrolment in the study: ≥ 1 major item(s) or ≥ 3 minor items or ≥ 2 kidney-related items. The majority of patients (81% in the avacopan arm, 82% in the prednisone arm) had renal involvement at baseline. However, the estimated glomerular filtration rate (eGFR) could not be less than 15 ml/min/1.73 m² at study entry and there could be no dialysis requirement, so that no data are available for these patients for the present therapeutic indication. In addition, patients with alveolar haemorrhage requiring invasive ventilation were excluded.

Patients were allocated in a 1:1 ratio and stratified according to "background therapy" (RTX vs CYC), "ANCA specificity" (MPO vs PR3) and "AAV status" (newly diagnosed vs relapsed) to either treatment with avacopan or treatment with prednisone, each in combination with placebo.

In the intervention arm, avacopan was used for 52 weeks according to the product information (30 mg twice daily). In the comparator arm, patients received 60 mg/day of prednisone at the start of the study, which was reduced to 5 mg/day over a period of 14 weeks and completely phased out after a total of 20 weeks.

In guidelines[2,3,4], a reduction of the glucocorticoid dosage below the Cushing's threshold is discussed as a long-term goal. However, according to clinical experts, the complete phasing out of glucocorticoids has also become established as a therapeutic goal in clinical care. Overall, however, the chosen glucocorticoid tapering regimen seems to be a fast-track approach compared to current guidelines.

Glucocorticoids not used in the study had to be avoided as much as possible during the study period. However, the use of glucocorticoids was allowed because of a comorbidity requiring treatment (such as adrenal insufficiency) or disease deterioration, the disease failed to improve or recurred. The percentage of subjects taking glucocorticoids as concomitant medication (includes all glucocorticoids not administered in the study) was 86% in the avacopan arm and 91% in the prednisone arm.

In both study arms, patients received background therapy: Either rituximab weekly for the first 4 weeks or cyclophosphamide (intravenous or oral) for the first 13 or 14 weeks respectively, followed by maintenance treatment with azathioprine or mycophenolate mofetil, as appropriate, until the end of the study. Combination therapy with rituximab was used more frequently in the ADVOCATE study (65% of patients). Contrary to current guideline recommendations, no maintenance treatment was initiated following treatment with rituximab.

Endpoints recorded in the ADVOCATE study included the percentage of patients in remission (after 26 weeks) and in sustained remission (after 52 weeks). Other patient-relevant endpoints were assessed in the categories of health-related quality of life and side effects.

[2] Yates M, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75(9):1583-1594.
[3] Schirmer et al. S1 guideline diagnostics and therapy of ANCA-associated vasculitis. Journal of Rheumatology 2017; 76: 77–104
[4] Mendel A, et al. CanVasc consensus recommendations for the management of antineutrophil cytoplasm antibody-associated vasculitis: 2020 update. J Rheumatol 2021;48(4):555-566.

Mortality

No endpoint was evaluated in the category "mortality". Fatalities were recorded as part of the safety assessment. By the end of the study, 2 (1%) deaths occurred in the avacopan arm and 4 (2%) deaths in the prednisone arm.

Morbidity

Remission and sustained remission

Both remission and maintenance of remission are central therapeutic goals in the present therapeutic indication and of high clinical relevance. The pharmaceutical company operationalises the endpoint "remission" as the achievement of a Birmingham Vasculitis Activity Score (BVAS) of 0 at week 26 without taking glucocorticoids for the treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis in the 4 weeks prior to week 26. "Sustained remission" was defined as remission at week 26 with no recurrence until week 52, a BVAS of 0 to week 52, and no use of glucocorticoids to treat ANCA-associated vasculitis in the 4 weeks before week 52.

The BVAS is an instrument for measuring disease activity in subjects with systemic vasculitis, which is completed by medical staff. The BVAS is divided into 9 organ-based systems, with each section containing symptoms or signs that are typical of the involvement of the respective organ in systemic vasculitis. Although the BVAS also includes items whose assessment is based on imaging and laboratory parameters that are not per se patient-relevant when considered individually, the absence of any disease activity (BVAS = 0) is considered patient-relevant. The endpoints are therefore used for the benefit assessment.

In the avacopan arm, 72% of subjects achieved remission at week 26, and 70% in the prednisone arm. For the endpoint "remission", there was no statistically significant difference between the study arms.

"Sustained remission" was achieved by 66% of patients in the avacopan arm and 55% in the prednisone arm. Based on the stratified 1-sided p value, there was a statistically significant difference in the benefit of avacopan compared with prednisone for this endpoint. The relative risk and confidence interval based on an analysis adjusted for the three stratification factors at randomisation were not provided by the pharmaceutical company despite prespecification. However, since the p value of the adjusted analysis speaks for a statistically significant difference in favour of avacopan, no consequences result from this.

For the endpoint "sustained remission", there was also a statistically significant interaction between treatment and the subgroup feature "AAV status" (non-stratified analysis). For the subgroup of patients with newly diagnosed ANCA-associated vasculitis, there was no statistically significant difference between the study arms. For the subgroup with recurrent ANCA-associated vasculitis, however, there was a statistically significant difference to the benefit of avacopan. Patients with recurrent ANCA-associated vasculitis predominantly (88%) received rituximab as background therapy. As it cannot be ruled out that the type of background therapy influenced this result and no statistically significant interaction was shown for the subgroup feature for other endpoints used in the benefit assessment, the effect modification is not taken into account for the present benefit assessment.

Recurrences

The occurrence of recurrences associated with the appearance of noticeable symptomatology is considered patient-relevant. The endpoint "relapse" was operationalised as a deterioration

of ANCA-associated vasculitis after achieving remission at week 26. The classification as relapse in the ADVOCATE study was made in the case of recurrence:

- ≥ 1 major item in the BVAS (e.g., item "increase in serum creatinine by 30% or reduction in creatinine clearance by > 25%") or
- ≥ 3 minor items in the BVAS (e.g., items "infiltrates", "proteinuria" and "haematuria") or
- 1 or 2 minor items in the BVAS on 2 consecutive visits.

A classification as a relapse can therefore be based exclusively on imaging procedures and laboratory parameters. A symptomatology perceptible to patients need not be present in this operationalisation. It is not possible to estimate the percentage of subjects with relapse who were diagnosed on the basis of asymptomatic findings that were not directly patient-relevant. Overall, only a few recurrences occurred during the course of the study.

The analyses for the endpoint "relapse" can also only be interpreted to a limited extent, as the percentage of subjects with a relapse and the time to occurrence of a relapse depend on characteristics such as "achievement of remission" and "time to remission", which can only be recorded after randomisation. This may not ensure that the structural equality of the study arms achieved by randomisation is maintained.

The relapse endpoint is therefore not used for the present benefit assessment.

Falling below the Cushing's threshold

Reducing the dosage of glucocorticoids, especially permanently falling below the Cushing's threshold, is of particular importance in the present therapeutic indication since the use of glucocorticoids, especially in high dosages over prolonged periods can lead to frequent occurrence of side effects and long-term consequences. The permanent reduction in the dosage of glucocorticoids below the so-called Cushing's threshold is therefore considered a relevant surrogate for the avoidance of glucocorticoid-induced side effects.

As part of the written statement, the pharmaceutical company provided post hoc analyses on the endpoint "Cushing's threshold" operationalised as the percentage of subjects in whom the average intake of glucocorticoids was reduced from ≥ 7.5 mg/day between day 1 and week 26 to < 7.5 mg/day between week 26 and week 52.

However, the data presented are contradictory overall and are therefore not used in the present benefit assessment.

Health status (EQ-5D VAS)

Health status was assessed in the ADVOCATE study using the visual analogue scale of the European Quality of Life -5-Dimensions (EQ-5D-VAS). There was no statistically significant difference between the treatment arms at week 26. However, there was a statistically significant difference to the advantage of avacopan compared with prednisone by week 52. The 95% CI of the standardised mean difference (SMD) in the form of Hedges' g is not completely outside the irrelevance range of -0.2 to 0.2, so that the clinical relevance of this effect cannot be assessed.

Renal function (eGFR)

The evaluation of renal function, assessed by estimated glomerular filtration rate (eGFR), was only performed in patients with renal involvement at baseline (≥ 1 kidney-related item of the BVAS). Due to this operationalisation, it remains unclear whether the eGFR of patients without kidney involvement at baseline deteriorated in the course of the study. In addition, the analyses presented for the endpoint "renal function" can only be interpreted to a limited extent, as this was only evaluated in subjects with kidney involvement at baseline and thus, the structural equality of the study arms achieved through randomisation could possibly not be maintained.

The endpoint "renal function" is not used for the present benefit assessment.

Quality of life

In the ADVOCATE study, health-related quality of life was assessed using the component score of the Short Form-36 Health Survey (SF-36).

While there was no statistically significant difference between the study arms for the mental component score (MCS) at weeks 26 and 52, there was a statistically significant difference for the physical component score (PCS) at both weeks 26 and 52 to the advantage of avacopan. The 95% CI of the SMD in the form of Hedges' g is not completely outside the irrelevance range of -0.2 to 0.2, so that the clinical relevance of this effect cannot be assessed.

Side effects

Adverse events (AEs) occurring from the first dose of study medication on day 1 until week 60, i.e., including the follow-up of 8 weeks after the end of treatment, were considered for the evaluations of the endpoints of the category "side effects".

There were no statistically significant differences between treatment arms for the overall rates of serious adverse events (SAEs) and events leading to discontinuation of study medication.

For AEs, at the MedDRA system organ class (SOC) and preferred term (PT) level, there was a statistically significant difference to the advantage of avacopan compared with prednisone for SOCs "eye disorders", "benign, malignant and non-specific neoplasms (including cysts and polyps)" and "endocrine disorders".

The pharmaceutical company does not submit a statistical evaluation for severe AEs. The results on severe AEs are therefore not assessable.

For SAEs, there were no statistically significant differences between the study arms at the SOC and PT level.

The percentage of subjects with an "AE of interest" was similar between the study arms in the categories "Infections", "Increased values in liver function tests", "Decreased leukocyte count" and "Hypersensitivity" defined by the pharmaceutical company.

Overall, the results of the side effects category are subject to uncertainty as the pharmaceutical company did not provide evaluations in which events related to the underlying disease (captured via the PT "Anti-neutrophil cytoplasmic antibody-positive vasculitis") were excluded from the overall rates of AEs, severe AEs (grade ≥ 3), SAEs and discontinuations due to AEs.

Overall assessment / conclusion

For the benefit assessment of avacopan for the treatment of adults with severe active GPA or MPA, results of the randomised controlled trial ADVOCATE are available on the endpoint categories of mortality, morbidity, quality of life and on side effects compared to prednisone. In both study arms, patients additionally received either cyclophosphamide (followed by azathioprine or mycophenolate mofetil) or rituximab as background therapy, as well as glucocorticoids, if necessary.

There was neither an advantage nor a disadvantage in the mortality endpoint category.

In the category of morbidity, there is a statistically significant advantage in favour of avacopan for the patient-relevant endpoint "sustained remission", while there were neither advantages nor disadvantages for the endpoint "remission". For the endpoint "health status", a statistically significant difference to the advantage of avacopan was observed at week 52, although the clinical relevance of this effect cannot be assessed.

For health-related quality of life assessed by the SF-36, there was no statistically significant difference between avacopan and prednisone for the mental component score. A statistically significant advantage was observed for the physical component score at weeks 26 and 52, although the clinical relevance cannot be assessed.

With regard to side effects, neither an advantage nor a disadvantage can be found for avacopan compared to prednisone, in each case in combination with a cyclophosphamide or rituximab treatment regimen. In detail, for AEs at the SOC and PT level, there was a statistically significant difference to the advantage of avacopan compared with prednisone for "eye disorders", "benign, malignant and non-specific neoplasms (including cysts and polyps)" and "endocrine disorders".

In the overall analysis, a minor additional benefit can be identified for avacopan, based on the statistically significant benefit in the morbidity endpoint "sustained remission".

Significance of the evidence

For the randomised controlled trial ADVOCATE on which the present benefit assessment is based, the risk of bias at study level is assessed as low.

Contrary to current guideline recommendations, uncertainties arise mainly due to the lack of maintenance treatment following initial treatment with rituximab.

In order to be able to depict the sustainability of the effects, in particular the maintenance of remission, a prolonged study duration would also have been necessary, also taking into account the statements of the clinical experts and the comments of the Public Assessment Report of the EMA (EPAR).

Overall, the uncertainties mentioned with regard to the significance of the evidence result in a hint for an additional benefit.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Tavneos with the active ingredient avacopan. The medicinal product Tavneos was approved

as an orphan drug. Avacopan is indicated in combination with a rituximab or cyclophosphamide dosing scheme for the treatment of adult patients with severe active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

The results of the 52-week randomised controlled trial ADVOCATE, in which avacopan was compared with prednisone in addition to a cyclophosphamide or rituximab treatment regimen, were used for the present benefit assessment.

In the endpoint category of mortality, there was no difference between the treatment arms. For the patient-relevant morbidity endpoint "sustained remission" at week 52, there is a statistically significant advantage in favour of avacopan, while for the endpoint "remission" there were neither advantages nor disadvantages. For the endpoint "health status", a statistically significant difference to the advantage of avacopan was observed at week 52, but the clinical relevance cannot be assessed.

For health-related quality of life assessed by the SF-36, there was no statistically significant difference between avacopan and prednisone for the mental component score. For the physical component score, on the contrary, a statistically significant advantage was observed at weeks 26 and 52, but the clinical relevance cannot be assessed.

With regard to side effects, there is neither an advantage nor a disadvantage for avacopan compared to prednisone, in each case in combination with a cyclophosphamide or rituximab treatment regimen.

Contrary to current guideline recommendations, uncertainties arise mainly due to the lack of maintenance treatment following initial treatment with rituximab. In addition, prolonged study duration would have been necessary to be able to map the sustainability of the effects, especially the maintenance of remission.

The overall conclusion is that there is a hint for a minor additional benefit of avacopan in combination with a rituximab or cyclophosphamide dosing scheme.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI). The data follow the representations of the pharmaceutical company and the assessment of IQWiG.

Overall, the pharmaceutical company's information on the number of patients in the SHI target population are to be classified as uncertain. The main reasons for this are the use of incomprehensible percentage values and assumptions, as well as the operationalisation of a severe, active form of disease chosen by the pharmaceutical company.

2.3 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: 4 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 studied 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, serious infections, malignancies and cardiovascular events, a Post-Authorisation Safety Study (PASS) was required by the EMA upon marketing authorisation.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Avacopan in combination with a rituximab or cyclophosphamide dosing scheme				
Avacopan in combination with rituximab and glucocorticoids, if necessary				
Avacopan	2 x daily	365	1	365
Rituximab	Day 1, 8, 15 and 22 of a 28-day cycle	1	4	4
Prednisolone	1 x daily	Varies from patient to patient	1	Different from patient to patient
Avacopan in combination with cyclophosphamide (intravenous)[5] and glucocorticoids, if necessary				
Avacopan	2 x daily	365	1	365

[5] 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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cyclophosphamide IV	Day 1 of a 14 - 21-day cycle	4.3 – 6.5[6]	1	4.3 – 6.5s
Prednisolone	1 x daily	Different from patient to patient	1	Different from patient to patient
Avacopan in combination with cyclophosphamide (peroral)[5] and glucocorticoids, if necessary				
Avacopan	2 x daily	365	1	365
Cyclophosphamide p.o.	1 x daily	98[7]	1	98
Prednisolone	1 x daily	Different from patient to patient	1	Different from patient to patient

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[8]

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The dosage of oral corticosteroids is used patient-individually in the course of treatment and does not follow a specific standard dosage. From the group of glucocorticoids, prednisolone was shown as an example with the potencies 5 mg and 20 mg for economic reasons. In addition, there are packs with a potency of 1 mg, 2 mg, 10 mg and 50 mg.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Avacopan in combination with a rituximab or cyclophosphamide regimen					
Avacopan in combination with rituximab and glucocorticoids, if necessary					
Avacopan	10 mg or 20 mg	30 mg	3 x 10 mg	365	1095 x 10 mg

[6] A maximum duration of 13 weeks = 91 days is used.
[7] A maximum duration of 14 weeks = 98 days is used.

[8] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	4	12 x 100 mg + 4 x 500 mg
Prednisolone	Different from patient to patient				
Avacopan in combination with cyclophosphamide (intravenous)[5] and glucocorticoids, if necessary					
Avacopan	10 mg or 20 mg	30 mg	3 x 10 mg	365	1095 x 10 mg
Cyclophosphamide IV	15 mg/kg BW = 1,155 mg	1,155 mg	(1 x 1,000 mg + 1 x 200 mg) - 3 x 500 mg	4.3 – 6.5	(4.3 x 1,000 mg + 4.3 x 200 mg) - 19.5 mg x 500 mg
Prednisolone	Different from patient to patient				
Avacopan in combination with cyclophosphamide (peroral)[5] and glucocorticoids, if necessary					
Avacopan	10 mg or 20 mg	30 mg	3 x 10 mg	365	1095 x 10 mg
Cyclophosphamide p.o.	2 mg/kg = 154 mg	154 mg	3 x 50 mg[9]	98	294 x 50 mg
Prednisolone	Different from patient to patient				

[9] The tablets cannot be divided into equal doses.

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Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Avacopan 10 mg	180 HC	€ 8,620.72	€ 1.77	€ 489.04	€ 8,129.91
Cyclophosphamide 50 mg[10]	100 CTA	€ 49.75	€ 1.77	€ 0.00	€ 47.98
Cyclophosphamide 200 mg	10 PSI	€ 62.87	€ 1.77	€ 2.86	€ 58.24
Cyclophosphamide 500 mg	6 PSI	84.55	€ 1.77	€ 9.28	€ 73.50
Cyclophosphamide 1,000 mg	6 PSI	€ 127.65	€ 1.77	€ 6.44	€ 119.44
Prednisolone 5 mg[10]	100 TAB	€ 15.40	€ 1.77	€ 0.33	€ 13.30
Prednisolone 20 mg[10]	100 TAB	€ 21.59	€ 1.77	€ 0.82	€ 19.00
Rituximab 100 mg	2 CIS	€ 717.18	€ 1.77	€ 33.50	€ 681.91
Rituximab 500 mg	1 CIS	€ 1,777.30	€ 1.77	€ 84.18	€ 1,691.35
Abbreviations: HC = hard capsules, CIS = concentrate for the preparation of an infusion solution, PSI = powder for solution for injection, TAB = tablets, CTA = coated tablets					

LAUER-TAXE® last revised: 15 July 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy, the costs incurred for this must be taken into account as costs for

[10] Fixed reimbursement rate

additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Diagnosis of hepatitis B infection

Patients should be tested for HBV infection before starting treatment with rituximab.

Premedication for prevention

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Designation of the therapy	Type of service	Costs/ pack/ service	Treatment days/ year	Annual treatment costs/ patient
Medicinal product to be assessed: Avacopan				
Not applicable				
Combination therapy				
Rituximab	*HBV test* Hepatitis B surface antigen status (GOP number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90
	Premedication Antihistamines e.g., dimetindene IV 1 mg/ 10 kg = 7.7 mg each 5 SFI	€ 15.32[11]	4	€ 30.64
	Antipyretics e.g., paracetamol oral 1,000 mg 10 TAB[6]	€ 0.97[12]	4	€ 0.97
	Methylprednisolone 100 mg 10 TAB		1 - 4	€ 58.02

[11] After deduction of the statutory rebates according to Sections 130 and 130a SGB V

[12] Calculated from the pharmacy sales price of € 1.06 minus € 0.05 (deduction according to Section 130 SGB V) and € 0.04 (deduction according to Section 130 a SB V).

		€ 58.02[13]		

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 11 February 2022, the pharmaceutical company submitted a dossier for the benefit assessment of avacopan to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 16 May 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 7 June 2022.

The oral hearing was held on 27 June 2022.

An amendment to the benefit assessment with a supplementary assessment was submitted on 7 July 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

[13] After deduction of the legally prescribed rebates according to Sections 130 and 130a SGB V, taking into account a combination of 40 mg + 16 mg + 4 mg tablets.

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 26 July 2022, and the draft resolution was approved.

At its session on 4 August 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 May 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	15 June 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 June 2022	Conduct of the oral hearing
Working group Section 35a	6 July 2022 20 July 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	27 July 2022	Concluding discussion of the draft resolution
Plenum	4 August 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 August 2022

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

Prof. Hecken