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)
Voclosporin (lupus nephritis)

of 17 August 2023

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient voclosporin on 1 March 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 24 February 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 June 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of voclosporin compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements

submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of voclosporin.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Voclosporin (Lupkynis) in accordance with the product information

Lupkynis is indicated in combination with mycophenolate mofetil for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN).

Therapeutic indication of the resolution (resolution of 17.08.2023):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with active class III, IV or V (including mixed classes III/V and IV/V) lupus nephritis, in combination with mycophenolate mofetil

Appropriate comparator therapy for voclosporin

- A patient-individual therapy taking into account any previous therapy and the disease activity, selecting the following active ingredients:

glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, mycophenolate mofetil/ mycophenolenic acid[2]

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section

[1] General Methods, version 6.1 of 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.
[2] See resolution on an amendment of the Pharmaceuticals Directive (AM-RL) of Annex VI - Off-Label-Use of mycophenolate mofetil/ mycophenolenic acid for lupus nephritis.

12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO:

on 1. For the treatment of lupus nephritis, eligible medicinal products approved for the underlying disease of systemic lupus erythematodes or specifically for lupus nephritis are: non-steroidal anti-inflammatory drugs (NSAIDs) (including ibuprofen, indomethacin), systemic glucocorticoids, azathioprine, antimalaria active ingredients (chloroquine and hydroxychloroquine), cyclophosphamide and belimumab

on 2. A non-medicinal treatment is unsuitable in the therapeutic indication.

on 3. In the therapeutic indication under consideration here, the following resolution of the G-BA is available:

- Resolution on an amendment to the Pharmaceuticals Directive (AM-RL) of Annex VI - Off-label use of mycophenolate mofetil/ mycophenolenic acid in lupus nephritis

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V". The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Lupus nephritis is a form of systemic lupus erythematosus that can be associated with serious complications.

Based on the evidence synopsis, no uniform therapy algorithm for the treatment of lupus nephritis can be derived at this time. The included EULAR/ ERA-EDTA guideline of 2019 ("Update of the Joint European League Against Rheumatism and European Renal Association- European Dialysis and Transplant Association) recommends initial treatment with mycophenolate mofetil in combination with glucocorticoids; in certain patient groups, initial therapy with cyclophosphamide may also be considered. Co-

administration of hydroxychloroquine is also recommended. For maintenance therapy, treatment with mycophenolate mofetil or azathioprine, together with hydroxychloroquine and, if necessary, glucocorticoids, is recommended depending on the previous therapy.

Based on the resolution of 21 September 2017 on an amendment to the Pharmaceuticals Directive (AM-RL) of Annex VI - Off-label use of mycophenolate mofetil/ mycophenolenic acid in lupus nephritis, the active ingredient mycophenolate mofetil can be prescribed off-label in accordance with Section 30, paragraph 1 of Section K of the AM-RL for possible use in lupus nephritis.

The present therapeutic indication for active class III, IV or V (including mixed classes III/V and IV/V) lupus nephritis includes both induction and maintenance therapy. It is assumed that the therapeutic indication includes both therapy naive and therapy experienced patients with active lupus nephritis. In the present therapeutic indication planned, a moderate to severe disease activity is assumed.

In the written statement procedure, the scientific-medical societies named the administration of glucocorticoids and chloroquine or hydroxychloroquine and mycophenolate mofetil or cyclophosphamide followed by maintenance therapy with mycophenolate mofetil or azathioprine as the previous therapy standard in the present therapeutic indication within the induction therapy. The immunosuppressant used in induction therapy or maintenance therapy depends on the individual patient. However, immunosuppressive therapy with mycophenolate mofetil is predominantly used in everyday clinical practice in Germany. The active ingredients tacrolimus and belimumab could be considered as add-on therapy in case of insufficient response to the standard therapy. Depending on the extent of the proteinuria of the patients in the therapeutic indication, the administration of an appropriate add-on therapy primarily with tacrolimus and possibly also with belimumab could also make sense at an earlier point in time.

The statements of the clinical experts in the written statement procedure thus support the available evidence. Tacrolimus is not approved for the treatment of lupus nephritis or for the treatment of the underlying disease of systemic lupus erythematosus. Belimumab has been approved for lupus nephritis since April 2021. The present guidelines do indicate, with a weak recommendation, that belimumab can be considered as an add-on for non-responsive or refractory disease, but no clear recommendations for induction or maintenance therapy can be derived. Belimumab is therefore considered as not being part of the appropriate comparator therapy.

In summary, for the treatment of lupus nephritis, patient-individual therapy considering glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine and mycophenolate mofetil is determined as appropriate comparator therapy.

For the implementation of patient-individual therapy in a direct comparator study, it is expected that the study doctor will have a choice of several treatment options that will allow a patient-individual treatment decision to be made, taking into account the criteria mentioned (multi-comparator study).

The marketing authorisation of the medicinal products must be taken into account. The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of voclosporin is assessed as follows:

Adults with active class III, IV or V (including mixed classes III/V and IV/V) lupus nephritis, in combination with mycophenolate mofetil

For adults with active class III, IV or V (including mixed classes III/V and IV/V) lupus nephritis, in combination with mycophenolate mofetil, an additional benefit is not proven.

Justification:

The pharmaceutical company uses results from an adjusted indirect comparison of voclosporin with belimumab via the bridge comparator placebo in combination with immunosuppressive basic therapy for its assessment. The AURORA-2 or AURA-LV and AURORA-1 voclosporin studies as well as the BLISS-LN belimumab study form the basis of the adjusted indirect comparison. However, the pharmaceutical company did not prepare the respective data or results of the individual AURA-LV and AURORA-1 studies in the dossier and accordingly did not use them to derive an additional benefit.

The AURORA-2 or AURA-LV and AURORA-1 voclosporin studies are described below.

AURA-LV study

The AURA-LV study is a randomised, controlled, double-blind phase 2 study that enrolled a total of 265 patients aged 18-75 years with active class III, IV and V (including mixed class III/V and IV/V) lupus nephritis. Patients were randomly assigned in a 2:2:1:1 ratio to either treatment with voclosporin (treatment arm A: N = 89), voclosporin high-dose (treatment arm B: N = 88) or assigned to one of the corresponding comparator arms with placebo (treatment arms C and D: total N = 88). The therapy with high-dose voclosporin in treatment arm B does not correspond to the specifications in the product information. Randomisation was stratified by biopsy class (pure class V vs other) and mycophenolate mofetil use at screening (yes vs no). In all study arms, patients received concomitant immunosuppressive therapy with mycophenolate mofetil and glucocorticoids in addition to voclosporin or placebo, according to a specific dosing scheme determined according to the study design. If the patients were already receiving treatment with mycophenolate mofetil before the start of the study, this should be continued at a stable dose during the study. Dose adjustments or interruptions were only allowed in case of clearly substantiated safety concerns. Cyclophosphamide, biologics (e.g. belimumab, rituximab), calcineurin inhibitors (e.g. ciclosporin, tacrolimus), immunoglobulins and other immunosuppressants were not allowed as concomitant

medication. Anti-malarial medicinal products should be administered additionally as concomitant therapy, provided there were no contraindications.

The primary endpoint of the AURA-LV study was evaluated at week 24 and was defined as confirmed UPCR ≤ 0.5 mg/mg and either eGFR ≥ 60 ml/min/1.73 m^2 or no confirmed decrease in eGFR ≥ 20% from baseline.

The duration of treatment in the study was 48 weeks. The study was conducted in several countries around the world between June 2014 and January 2017.

AURORA-1 study

The AURORA-1 study is a randomised, controlled, double-blind phase 3 study comparing voclosporin with placebo, which enrolled a total of 357 patients aged 18-75 years with active class III, IV and V (including mixed class III/V and IV/V) lupus nephritis and a diagnosis of SLE (according to the 1997 ACR criteria). Randomisation in a 1:1 ratio randomly to treatment with voclosporin (N = 179) or placebo (N = 178) was stratified by biopsy class (pure class V vs other) and mycophenolate mofetil use at screening (yes vs no). The patients received an immunosuppressive concomitant therapy with mycophenolate mofetil and glucocorticoids in addition to voclosporin or placebo. The specifications for the defined dosing scheme as well as for pre- and concomitant treatment largely corresponded to those of the AURA-LV study.

After completion of the 52-week treatment in the AURORA-1 study, the patients had the option of continuing their therapy (voclosporin or placebo, in each case in combination with the concomitant medication received in the AURORA-1 study) in the AURORA-2 extension study.

The primary endpoint of the AURORA-1 study was evaluated at week 52 and was defined as UPCR ≤ 0.5 mg/mg and either eGFR ≥ 60 ml/min/1.73 m^2 or no confirmed decrease in eGFR > 20% from baseline.

The study was conducted in several countries around the world between March 2017 and October 2019.

AURORA-2 study

In the AURORA-2 extension study, 216 of the 357 patients randomised in the AURORA-1 study participated (intervention arm vs comparator arm, n [%]): 116 [65%] vs 100 [56%]). The reduced number is due, among other things, to the fact that some of the patients discontinued treatment with the study medication prematurely in the AURORA-1 study (intervention arm vs comparator arm, n [%]): 43 [24%] vs 59 [33%]). In addition, not all patients took the opportunity to participate in the AURORA-2 extension study after the 52-week treatment in the AURORA-1 study.

The study was conducted in several countries around the world between September 2019 and October 2021. For the AURORA-2 study, there is no randomised comparison with the appropriate comparator therapy.

For its submitted adjusted indirect comparison of voclosporin with belimumab via the bridge comparator placebo in combination with concomitant immunosuppressive therapy, the pharmaceutical company conducts 4 types of analyses based on the AURORA-2 or AURA-LV and AURORA-1 voclosporin studies as well as the BLISS-LN belimumab study (one main analysis and 3 sensitivity analyses), each taking into account different evaluation times and endpoints.

For its main analysis, the pharmaceutical company uses results at the end of the AURORA-2 study for the intervention (treatment duration of 3 years in total [including the treatment in the AURORA-1 study]) and results at the end of the BLISS-LN study (treatment duration of 2 years) for the comparator therapy. The pharmaceutical company shall submit these analyses for selected endpoints of the categories mortality, morbidity and side effects.

The pharmaceutical company deviates from the G-BA's determination and names only belimumab as the appropriate comparator therapy. It justifies this in particular by stating that the selection of active ingredients named by the G-BA for patient-individual therapy cannot be regarded as adequate and modern lupus nephritis therapy due to their toxicity and lack of efficacy. A recommendation for belimumab is also increasingly finding its way into corresponding guidelines, which are currently being updated, and a therapy with belimumab is also established in everyday care.

The present therapeutic indication for active class III, IV or V (including mixed classes III/V and IV/V) lupus nephritis includes both induction and maintenance therapy. It is assumed that the therapeutic indication includes both therapy naive and therapy experienced patients with active lupus nephritis. On the basis of the available evidence in the therapeutic indication and taking into account the participation of the scientific-medical societies, the G-BA, as stated above, determined a patient-individual therapy taking into account any previous therapy and the disease activity, selecting glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, mycophenolate mofetil. For the implementation of patient-individual therapy in a direct comparator study, it is expected that the study doctor will have a choice of several treatment options that will allow a patient-individual treatment decision to be made, taking into account the criteria mentioned.

The indirect comparison of voclosporin versus belimumab submitted by the pharmaceutical company is not relevant for the present benefit assessment due to the deviation from the specific appropriate comparator therapy for the benefit assessment.

In addition, the pharmaceutical company did not prepare the respective data or results of the individual AURA-LV and AURORA-1 voclosporin studies in the dossier and did not use them to derive an additional benefit, so that they cannot be considered for the benefit assessment either.

In summary, no suitable data were presented for the assessment of the additional benefit of voclosporin compared to the appropriate comparator therapy determined by the G-BA, a patient-individual therapy, taking into account any previous therapy and the disease activity, selecting glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine, mycophenolate mofetil. An additional benefit is correspondingly not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Lupkynis" with the active ingredient voclosporin. Voclosporin indicated in combination with mycophenolate mofetil for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN). The G-BA determined a patient-individual therapy as an appropriate comparator therapy, taking into account any previous therapy and disease activity, if applicable, and selecting glucocorticoids, azathioprine, cyclophosphamide, hydroxychloroquine, chloroquine and mycophenolate mofetil.

The pharmaceutical company uses results from an adjusted indirect comparison of voclosporin with belimumab via the bridge comparator placebo in combination with immunosuppressive basic therapy for its assessment. The AURORA-2 or AURA-LV and AURORA-1 voclosporin studies as well as the BLISS-LN belimumab study form the basis of the adjusted indirect comparison.

The indirect comparison of voclosporin versus belimumab submitted by the pharmaceutical company is not relevant for the present benefit assessment due to the deviation from the specific appropriate comparator therapy for the benefit assessment.

As the pharmaceutical company did not prepare the respective data or results of the individual AURA-LV and AURORA-1 voclosporin studies in the dossier and did not use them to derive an additional benefit, they cannot be considered for the benefit assessment either.

In summary, no suitable data were presented for the assessment of the additional benefit of voclosporin compared to the appropriate comparator therapy determined by the G-BA. An additional benefit is correspondingly not proven.

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 G-BA bases its resolution on the information from the dossier of the pharmaceutical company.

These figures are mathematically comprehensible. Overall, however, the stated number of patients in the SHI target population is fraught with uncertainty and tends to be underestimated for the following reasons, among others:

The lower limit set by the pharmaceutical company is based on a patient number from the previous dossier assessment on belimumab with a target population that deviates from the present therapeutic indication or is more restricted. The upper limit number is based on prevalence data from 2002, but a more recent publication suggests that the prevalence rate for patients with SLE may be higher. Since the pharmaceutical company does not explicitly operationalise the disease activity, there are uncertainties as to whether all relevant patients have been recorded with sufficient specificity when forming a range of patients with active lupus nephritis.

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 Lupkynis (active ingredient: voclosporin) at the following publicly accessible link (last access: 27 April 2023):

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

Treatment with voclosporin should only be initiated and monitored by doctors experienced in treating lupus nephritis.

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: 1 August 2023).

A total cumulative dose of 50 g chloroquine in adults should not be exceeded. This results in 322.5 treatment days for the daily dose of 250 mg chloroquine phosphate (corresponding to 155.02 mg chloroquine).

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 varies from patient to patient 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.

According to the product information, no recommendations are given on the duration of therapy with the glucocorticoids prednisone and prednisolone. The treatment duration depends on the individual patient's response and varies from patient to patient.

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				
Voclosporin	Continuously, 2 x daily	365.0	1	365.0
Mycophenolate mofetil[3]	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Patient-individual therapy taking into account any previous therapy and the disease activity, selecting the following active ingredients:				
Azathioprine	Continuously, 1 x daily	365.0	1	365.0
Cyclophosphamide	Continuously, 1 x daily	365.0	1	365.0
Hydroxychloroquine	Continuously, 1 x daily	365.0	1	365.0
Chloroquine phosphate	Continuously, 1 x daily	322.5	1	322.5
Mycophenolate mofetil	Continuously, 1 x daily	365.0	1	365.0
Glucocorticoids				
Prednisolone	Different from patient to patient			
Prednisone	Different from patient to patient			

[3] Resolution on an amendment to the Pharmaceuticals Directive (AM-RL) of Annex VI - Off-label use of mycophenolate mofetil/mycophenolenic acid in lupus nephritis

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

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.

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).[4]

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					
Voclosporin	23.7 mg	47.4 mg	6 x 7.9 mg	365.0	2,190 x 7.9 mg
Mycophenolate mofetil	1,000 mg - 2,000 mg	1,000 mg - 2,000 mg	2 x 500 mg - 4 x 500 mg	365.0	730 x 500 mg - 1,460 x 500 mg
Appropriate comparator therapy					
Patient-individual therapy taking into account any previous therapy and the disease activity, selecting the following active ingredients:					
Azathioprine	1 mg/kg BW - 3 mg/kg BW	77 mg - 231 mg	1 x 75 mg - 2 x 100 mg + 1 x 25 mg	365.0	365 x 75 mg - 730 x 100 mg + 365 x 25 mg
Cyclophosphamide	1 – 2 mg/kg BW	77 mg – 154 mg	2 x 50 mg - 3 x 50 mg	365.0	730 x 50 mg - 1,095 x 50 mg

[4] 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
Hydroxychloroquine	200 mg - 400 mg	200 mg - 400 mg	1 x 200 mg - 2 x 200 mg	365.0	365 x 200 mg - 730 x 200 mg
Chloroquine phosphate [5]	250 mg	250 mg	1 x 250 mg	322.5	322.5 x 250 mg
Mycophenolate mofetil	1,000 mg - 2,000 mg	1,000 mg - 2,000 mg	2 x 500 mg - 4 x 500 mg	365.0	730 x 500 mg - 1,460 x 500 mg
Glucocorticoids					
Prednisolone	40 mg – 100 mg	40 mg – 100 mg	2 x 20 mg - 2 x 50 mg	Different from patient to patient	
Prednisone	40 mg – 100 mg	40 mg – 100 mg	2 x 20 mg - 2 x 50 mg	Different from patient to patient	

[5] Chloroquine is currently only available on the German market as an import drug without any group association.

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					
Voclosporin 7.9 mg	180 SC	€ 1,635.58	€ 2.00	€ 154.49	€ 1,479.09
Mycophenolate mofetil 500 mg[6]	250 FCT	€ 409.91	€ 2.00	€ 31.53	€ 376.38
Appropriate comparator therapy					
Azathioprine 100 mg[6]	100 FCT	€ 57.98	€ 2.00	€ 3.69	€ 52.29
Azathioprine 25 mg[6]	100 FCT	€ 29.74	€ 2.00	€ 1.46	€ 26.28
Azathioprine 75 mg[6]	100 FCT	€ 49.79	€ 2.00	€ 3.05	€ 44.74
Cyclophosphamide 50 mg[6]	100 CTA	€ 49.75	€ 2.00	€ 0.00	€ 47.75
Chloroquine phosphate 250 mg	100 TAB	€ 28.20	€ 2.00	€ 0.00	€ 26.20
Mycophenolate mofetil 500 mg[6]	250 FCT	€ 409.91	€ 2.00	€ 31.53	€ 376.38
Prednisolone	Different from patient to patient				
Prednisone	Different from patient to patient				
Abbreviations: SC = soft capsules; FCT = film-coated tablets; CTA = coated tablets, TAB = tablets, PEN = solution for injection in a pre-filled pen					

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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 in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

[6] Fixed reimbursement rate

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.

Because there are no 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 in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

2.5 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 Voclosporin

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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

At its session on 25 January 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The appropriate comparator therapy was adjusted at the Medicinal Products Working Group session on 3 August 2022.

On 24 February 2023, the pharmaceutical company submitted a dossier for the benefit assessment of voclosporin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 27 February 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient voclosporin.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 May 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 June 2023. The deadline for submitting written statements was 22 June 2023.

The oral hearing was held on 10 July 2023.

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 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 was discussed at the session of the subcommittee on 8 August 2023, and the proposed resolution was approved.

At its session on 17 August 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 January 2022	Determination of the appropriate comparator therapy
Working group Section 35a	3 August 2022	Implementation of the appropriate comparator therapy
Working group Section 35a	4 July 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 July 2023	Conduct of the oral hearing
Working group Section 35a	18 July 2023 1 August 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	8 August 2023	Concluding discussion of the draft resolution
Plenum	17 August 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 August 2023

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

Prof. Hecken