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)
Zilucoplan (myasthenia gravis, AChR antibody+)

of 15 August 2024

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 all 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 zilucoplan on 1 March 2024 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 29 February 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 June 2024 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 zilucoplan compared with 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 zilucoplan.

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 Zilucoplan (Zilbrysq) in accordance with the product information

Zilbrysq is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Therapeutic indication of the resolution (resolution of 15 August 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with anti-acetylcholine receptor antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Appropriate comparator therapy for zilucoplan as an adjuvant treatment to standard therapy:

- Eculizumab (for refractory patients) or efgartigimod alfa or ravulizumab

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):</u>

on 1. In addition to zilucoplan, the active ingredients azathioprine, distigmine bromide, efgartigimod alfa, neostigmine methylsulphate, pyridostigmine bromide, ravulizumab, rozanolixizumab as well as the glucocorticoids prednisolone and prednisone are approved for the therapeutic indication of generalised myasthenia gravis. The antibody eculizumab is approved for refractory, generalised myasthenia gravis in AChR AB-positive patients.

on 2. Thymectomy can be considered as a non-medicinal treatment for the treatment of generalised myasthenia gravis.

on 3. For the therapeutic indication of generalised myasthenia gravis, resolutions on the benefit assessment of efgartigimod alfa according to Section 35a SGB V dated 16 February 2023 and of ravulizumab dated 20 April 2023 are available.

In addition, there are resolutions on the off-label use (Annex VI to Section K of the Pharmaceuticals Directive, Part A) of mycophenolate mofetil for the "long-term therapy of generalised myasthenia gravis in the case of therapy resistance under treatment with

the approved substances or in the case of azathioprine intolerance" and of intravenous immunoglobulins in "myasthenic crises/ severe exacerbations".

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 therapeutic indication.

Overall, the identified evidence in the therapeutic indication is very limited. This body of evidence comprises three systematic reviews and two additionally presented guidelines, including the German S2k guideline "Diagnosis and treatment of myasthenic syndromes"[2].

Recommendations of the above guidelines for patients with AChR AB-positive generalised myasthenia gravis include cholinesterase inhibitors and immunosuppressants (glucocorticoids, azathioprine, mycophenolate mofetil, ciclosporin A, methotrexate and tacrolimus), the thymectomy, complement inhibitors (eculizumab, ravulizumab), a neonatal Fc receptor inhibitor (efgartigimod alfa) and a CD-20 antibody (rituximab). In addition, intravenous immunoglobulins and plasmapheresis/ immunoabsorption may be used if the previously mentioned options fail.

Mycophenolate mofetil, ciclosporin A, methotrexate, tacrolimus, rituximab and intravenous immunoglobulins are not approved for the present therapeutic indication. However, according to Annex VI to the Pharmaceuticals Directive, mycophenolate mofetil is reimbursable in cases of therapy resistance under treatment with the approved substances or in cases of azathioprine intolerance, as well as intravenous immunoglobulins in cases of myasthenic crises/ severe exacerbations.

According to the current S2k guideline, treatment decisions are made in particular depending on disease activity and disease severity. The appropriate classification into mild/ moderate versus (highly) active generalised myasthenia gravis should be based on the severity of clinical symptomatology, their duration and tendency to regress, as well as clinical residuals and the presence or number of crisis-like exacerbations/ crises. Therapy-refractory generalised myasthenia gravis is subsumed under the (highly) active disease and is therefore not addressed separately in the treatment recommendations of the S2k guideline.

The G-BA defines a "standard therapy", as it is mentioned in the approved therapeutic indication for zilucoplan, as a therapy consisting of cholinesterase inhibitors and/or an immunosuppressive basic therapy (corticosteroids and non-steroidal immunosuppressants). According to the S2k guideline, this standard therapy can be considered for mild or moderate disease activity/ severity. An add-on to standard therapy for AChR AB-positive generalised myasthenia gravis is recommended for active or highly active generalised myasthenia gravis. This add-on therapy is used in particular as escalation therapy after failure to respond to standard therapy, but can also be an early treatment option in highly active courses of the disease. Eculizumab, efgartigimod alfa, ravulizumab and rituximab are named as the active ingredients of first choice.

As already described, rituximab is not approved for the present therapeutic indication and does not play a significant role in the current German medical treatment situation.

[2] Wiendl H., Meisel A. et al, Diagnostics and Therapy of Myasthenic Syndromes, S2k Guideline, 2022, DGN, in: German Society of Neurology (ed.), Guidelines for Diagnosis and Therapy in Neurology. Online: www.dgn.org/leitlinien (accessed 25.06.2024)

The orphan drug efgartigimod alfa was identified as having a considerable additional benefit by resolution of 16 February 2023. The additional benefit of the active ingredient ravulizumab was not proven by resolution of 20 April 2023.

The marketing authorisation of eculizumab is limited to the treatment of patients refractory to therapy and therefore only applies to a sub-population of the therapeutic indication.

Intravenous immunoglobulins as well as plasmapheresis or immunoabsorption are only recommended if the above-mentioned therapy options fail or as therapy for a myasthenic crisis and thus, represent a treatment setting other than the therapeutic indication of zilucoplan.

Even if the acute treatment of myasthenic crises and/or exacerbations are not specifically covered by the therapeutic indication, it must be ensured as part of a study that a myasthenic crisis and/or crisis-like deteriorations are optimally treated.

In addition to the medicinal treatment options, thymectomy also has a high priority in the therapy of AChR AB-positive generalised myasthenia gravis. However, it is assumed that patients for whom treatment with zilucoplan is indicated are either ineligible for thymectomy or have already undergone this.

The active ingredient rozanolixizumab is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 5 January 2024). Based on the generally accepted state of medical knowledge, rozanolixizumab is not determined to be an appropriate comparator therapy for the present resolution.

In the overall assessment, eculizumab (only for refractory patients) or efgartigimod alfa or ravulizumab are determined as the appropriate comparator therapy. The appropriate comparator therapy includes several therapy options. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the specified patient and disease characteristics. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

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 zilucoplan is assessed as follows:

The additional benefit is not proven for adults with anti-acetylcholine receptor antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy.

Justification:

The pharmaceutical company presented the results of the pivotal phase III MG0009 and MG0010 studies as well as meta-analyses of these studies to prove the additional benefit of zilucoplan. In addition, it presented a supplementary adjusted indirect comparison of zilucoplan with ravulizumab via the bridge comparator placebo.

The MG0009 and MG0010 studies are randomised double-blind studies comparing zilucoplan with placebo over a period of 12 weeks. The MG0009 and MG0010 studies as well as the meta-analyses presented are unsuitable for the benefit assessment, as they do not allow a comparison with the appropriate comparator therapy.

The indirect comparison presented additionally in the Annex to Module 4 cannot be used for the benefit assessment either, as the pharmaceutical company did not collect or present any information and the data processing does not meet the requirements for dossier submission.

In addition, the MG0009 and MG0010 studies and the indirect comparison only examined a treatment duration of 12 weeks.

The data presented by the pharmaceutical company are therefore unsuitable for the assessment of the additional benefit of zilucoplan compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Zilbrysq with the active ingredient zilucoplan.

Zilucoplan is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

The G-BA determined a therapy with eculizumab (for refractory patients) or efgartigimod alfa or ravulizumab as the appropriate comparator therapy.

For the assessment of additional benefit, the pharmaceutical company submitted the MG0009 and MG0010 RCTs as well as meta-analyses of these studies, in which zilucoplan was compared with placebo in each case. In addition, an indirect comparison with ravulizumab was presented.

The placebo comparison in the MG0009 and MG0010 studies does not represent a suitable implementation of the appropriate comparator therapy for the present therapeutic indication. The indirect comparison presented additionally in the Annex to Module 4 cannot be used for the benefit assessment either, as the pharmaceutical company did not collect or present any information and the data processing does not meet the requirements for dossier submission. In addition, the MG0009 and MG0010 studies and the indirect comparison only examined a treatment duration of 12 weeks.

An additional benefit of zilucoplan compared to the appropriate comparator therapy is therefore 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 present resolution is based on the information from the dossier of the benefit assessment procedure for the active ingredient efgartigimod alfa, which was ongoing at the time of drafting the resolution.

Overall, the stated number of patients in the SHI target population is subject to uncertainties for the lower limit and overestimated for the upper limit. This results, among other things, from the operationalisation of patients with high disease activity/ severity, which was carried out exclusively taking into account MGFA classes II to IV with reference to the highest degree

of severity ever achieved in the course of the disease. Nevertheless, a number at the lower end of the stated range is currently the most plausible estimate of patient numbers in the therapeutic indication of anti-AChR antibody-positive generalised myasthenia gravis.

In previous procedures in the therapeutic indication of anti-AChR antibody-positive generalised myasthenia gravis, a significantly higher number of patients (approx. 14,000 - 16,800) was determined for the active ingredient efgartigimod alfa by resolution of 16 February 2023 and a significantly lower number (800 - 1,200) for the active ingredient ravulizumab by resolution of 20 April 2023. The patient numbers in the resolution on the active ingredient efgartigimod alfa refer to all adults with generalised myasthenia gravis who are anti-AChR antibody-positive, without restriction to patients who are eligible for an add-on to standard therapy. The patient numbers in the resolution on the active ingredient ravulizumab, on the contrary, relate exclusively to refractory patients and therefore only represent part of the current target population.

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 zilbrysq (active ingredient: zilucoplan) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 25 June 2024):

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

Treatment with zilucoplan should only be initiated and monitored by doctors experienced in treating neuromuscular diseases.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card). In particular, the training material contains information and warnings regarding the increased risk of meningococcal infection under zilucoplan.

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 2024).

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.

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.

Adults with anti-acetylcholine receptor antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Treatment period:

The dosage recommended in the product information was used as the calculation basis.

One treatment cycle of efgartigimod alfa lasts 4 weeks. Further treatment cycles are administered on a patient-individual basis according to clinical assessment and at the earliest 7 weeks after the first infusion.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Zilucoplan	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Eculizumab (for refractory patients) or efgartigimod alfa or ravulizumab				
Eculizumab	Continuously, 1 x every 12-16 days	22.8 - 30.4	1	22.8 - 30.4
Efgartigimod alfa	1 x every 7 days per 4-week cycle	1 - 7.4	4	4 - 29.6
Ravulizumab	Continuously, 1 x every 56 days	6.5	1	6.5

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.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population"[3] were used as a basis (average body weight: 77.7 kg).

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					
Zilucoplan	32.4 mg	32.4 mg	1 x 32.4 mg	365.0	365 x 32.4 mg

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), 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
Appropriate comparator therapy					
Eculizumab (for refractory patients) or efgartigimod alfa or ravulizumab					
Eculizumab	1,200 mg	1,200 mg	4 x 300 mg	22.8 - 30.4	91.2 - 121.6 x 300 mg
Efgartigimod alfa	1,000 mg	1,000 mg	1 x 1,000 mg	4 - 29.6	4 - 29.6 x 1000 mg
Ravulizumab	3,300 mg	3,300 mg	3 x 1,100 mg	6.5	19.5 x 1,100 mg

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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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					
Zilucoplan 32.4 mg	28 SFI	€ 27,448.16	€ 2.00	€ 1,566.98	€ 25,879.18
Appropriate comparator therapy					
Eculizumab 300 mg	1 CIS	€ 5,877.85	€ 2.00	€ 335.09	€ 5,540.76
Efgartigimod alfa 1000 mg	1 SFI	€ 17,710.60	€ 2.00	€ 1,008.16	€ 16,700.44
Ravulizumab 1,100 mg	1 CIS	€ 18,004.15	€ 2.00	€ 1,027.63	€ 16,974.52
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection					

LAUER-TAXE® last revised: 15 July 2024

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.

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 need to be taken into account.

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 1.10.2009 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 agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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.

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

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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered

due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the

assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the

combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with anti-acetylcholine receptor antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

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

References:
Product information for zilucoplan (Zilbrysq); Zilbrysq 16.6 mg/ 23 mg/ 32.4 mg solution for injection in a pre-filled syringe; last revised: December 2023

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 23 February 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 9 January 2024.

On 29 February 2024, the pharmaceutical company submitted a dossier for the benefit assessment of zilucoplan to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 March 2024 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 zilucoplan.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 May 2024, and the written statement procedure was initiated with publication on the G-BA website on 3 June 2024. The deadline for submitting statements was 24 June 2024.

The oral hearing was held on 8 July 2024.

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 6 August 2024, and the proposed draft resolution was approved.

At its session on 15 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 February 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	9 January 2024	New determination of the appropriate comparator therapy
Working group Section 35a	3 July 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 July 2024	Conduct of the oral hearing

Working group Section 35a	17 July 2024 31 July 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	6 August 2024	Concluding discussion of the draft resolution
Plenum	15 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 August 2024

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

Prof. Hecken