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)
Efgartigimod alfa (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit (myasthenia gravis, AChR antibody+))

of 19 September 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 active ingredient efgartigimod alfa (Vyvgart) was listed for the first time on 1 September 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Vyvgart for the treatment of myasthenia gravis 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.

At its session on 16 February 2023, the G-BA decided on the benefit assessment of efgartigimod alfa in the therapeutic indication "Vyvgart is indicated as an add-on to standard therapy for the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive" in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an

amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Chapter 5 Section 5, paragraphs 1 to 6 Rules of Procedure (VerfO) within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 21 December 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 April 2024, due to exceeding the € 30 million turnover limit within the period from July 2022 to June 2023. The pharmaceutical company has submitted the final dossier to the G-BA in due time in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 VerfO on 28 March 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 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 efgartigimod alfa 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 efgartigimod alfa.

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 Efgartigimod alfa (Vyvgart) according to the product information

Vyvgart is indicated as an add-on to standard therapy for the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

Therapeutic indication of the resolution (resolution of 19 September 2024):

See therapeutic indication according to marketing authorisation.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for efgartigimod alfa as an add-on to standard therapy:

- Eculizumab (only for refractory patients) 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.
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.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. The active ingredients azathioprine, distigmine, neostigmine, pyridostigmine as well as the glucocorticoids prednisolone and prednisone are approved for the treatment of generalised masthenia gravis (gMG). In addition to efgartigimod alfa, the active ingredients eculizumab (for refractory patients), ravulizumab, rozanolixizumab and zilocuplan are also approved specifically for anti-AChR-positive gMG.

on 2. Thymectomy is considered as a non-medicinal treatment option for the treatment of gMG.

on 3. For the therapeutic indication of generalised myasthenia gravis, resolutions on the benefit assessment of ravulizumab according to Section 35a SGB V dated 20 April 2023 and of rozanolixizumab and zilucoplan each dated 15 August 2024 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 anti-AChR antibody-positive gMG 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.

[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)

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 gMG 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 gMG 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 efgartigimod alfa, 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 anti-AChR antibody-positive gMG is recommended for active or highly active gMG. 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.

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.

The active ingredients rozanolixizumab and zilucoplan, which are also approved as an add-on to standard therapy, are new treatment options that have only recently been approved for this therapeutic indication. By resolution of 15 August 2024, no additional benefit of the active ingredient zilucoplan compared with the appropriate comparator therapy was shown. At the same time, a hint for a considerable additional benefit was identified in an orphan drug assessment of the active ingredient rozanolixizumab in subjects with anti-AChR antibody-positive gMG. However, the significance of these active ingredients in everyday clinical care cannot be conclusively assessed as they have only been recently granted the marketing authorisation. Therefore, the two active ingredients rozanolixizumab and zilucoplan are not determined as appropriate comparator therapy.

Intravenous immunoglobulins and plasmapheresis or immunoabsorption are only recommended if the above-mentioned therapy options fail or as therapy for a myasthenic crisis. These options therefore represent a treatment setting different from the therapeutic indication of efgartigimod alfa.

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 anti-AChR antibody-positive gMG. However, it is assumed that patients for whom treatment with efgartigimod alfa is indicated are either ineligible for thymectomy or have already undergone this.

In the overall assessment, eculizumab (only for refractory patients) 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 efgartigimod alfa is assessed as follows:

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

Justification:

No direct comparator studies of efgartigimod alfa versus eculizumab or ravulizumab are available for adults with anti-AChR antibody-positive generalised Myasthenia Gravis (gMG) who are eligible for an add-on to standard therapy. In the dossier, the pharmaceutical company therefore presented two adjusted indirect comparisons according to Bucher via the placebo bridge comparator. The ADAPT study (ARGX-113-1704) is presented on the intervention side and the CHAMPION study (ALXN1210-MG-306) on the comparator side for ravulizumab and the REGAIN study (ECU-MG-301) for eculizumab in refractory subjects with gMG.

ADAPT study

The ADAPT study is a multicentre, double-blind, randomised controlled trial over 26 weeks in which the efficacy and safety of efgartigimod alfa was compared with placebo - in each case in combination with standard therapy.

Adults with gMG who had a Myasthenia Gravis Foundation of America (MGFA) classification II to IV were enrolled in the ADAPT study. The study participants had to continue to have disease-specific symptoms (*Myasthenia gravis - activities of daily living* (MG-ADL) score ≥ 5 points, more than 50% of the score due to non-ocular symptoms) with stable standard therapy.

The study population of the ADAPT study (n = 167) includes both patients with positive and negative anti-AChR antibody status. In accordance with the approved therapeutic indication of efgartigimod alfa, the pharmaceutical company presented evaluations of the sub-population of patients with positive anti-AChR antibody status in the dossier. Subjects enrolled in the ADAPT study received either placebo (n = 64 anti-AChR-antibody-positive) or efgartigimod alfa (n = 65 anti-AChR-antibody-positive) for at least one and up to three treatment cycles, depending on individual response.

If the patients experienced a clinical deterioration during the course of the study, emergency therapy was possible, but led to discontinuation of the study medication.

A treatment cycle consisted of a 3-week treatment phase and a 5-week follow-up period. A new treatment cycle was initiated depending on the patient's clinical response. Condition for a further cycle was loss of response, in case of response in the previous cycle, and a MG-ADL score of ≥ 5 points, with more than 50% of the total score attributable to non-ocular symptoms.

In addition, a new treatment cycle had to be started on day 127 at the latest in order to be completed within the 26-week study phase. Study participants who required another treatment cycle after day 127 had to enter the single-arm extension study ADAPT+ (ARGX-113-1705) prematurely. All patients who completed observation in the study after week 26 were also able to proceed to the ADAPT+ study.

Based on the information provided by the pharmaceutical company, it is unclear what percentage of patients entered the extension study prematurely due to the need for a new treatment cycle after day 127 and what percentage only entered after completion of the maximum planned duration of treatment and observation of 26 weeks. However, since the median duration of observation in both study arms was only 142 days (20.3 weeks), it can be assumed that a large percentage of patients must have entered the extension study before completing the maximum planned duration of treatment and observation.

The primary endpoint of the ADAPT study was the reduction in the MG-ADL score after the 1st treatment cycle compared to the start of the cycle.

CHAMPION study

The CHAMPION study is a randomised, controlled, double-blind phase 3 study in which ravulizumab was tested against placebo - in each case, in addition to the existing standard therapy - over 26 weeks.

175 adults with an MGFA classification of II to IV, a positive anti-AChR antibody status and an MG-ADL score of ≥ 6 points at the start of the study were enrolled.

Treatment was administered with an initial dose of ravulizumab or placebo on day 1, followed by a maintenance dose every 8 weeks from day 15. If the patients experienced a clinical deterioration during the course of the study, emergency therapy was administered at the discretion of the principal investigator.

The primary endpoint was the change in MG-ADL at week 26 compared to the start of the study.

REGAIN study

The REGAIN study is a randomised, controlled, double-blind, phase 3 study which investigated eculizumab compared to placebo – in each case in addition to standard therapy, if necessary – over 26 weeks.

The study enrolled 126 adults with refractory anti-AChR antibody-positive gMG who had an MGFA classification II to IV at the time of screening and an MG-ADL score ≥ 6 at the start of the study. Refractory disease was defined as follows: I) failed treatment for ≥ 1 year with ≥ 2 immunosuppressants (corticosteroids and non-steroidal immunosuppressants), i.e. persistent impairment of activities of daily living despite immunosuppressants or II) ≥ 1 failed treatment with immunosuppressants and chronic plasmapheresis/ chronic plasma exchange or chronic administration of intravenous immunoglobulins within the last 12 months.

Treatment was administered with an initial dose of placebo or eculizumab, followed by a maintenance dose every 2 weeks. If the patients experienced a clinical deterioration during the course of the study, the administration of emergency therapy was permitted at the doctor's discretion.

The primary endpoint was the change in MG-ADL at week 26 compared to the start of the study.

Adjusted indirect comparisons

For the assessment of the additional benefit of efgartigimod alfa compared with the appropriate comparator therapy, the pharmaceutical company presented results from two separate indirect comparisons. These are adjusted indirect comparisons - according to Bucher via the placebo bridge comparator - of efgartigimod alfa (ADAPT study) with either ravulizumab (CHAMPION study) or eculizumab (REGAIN study).

Differences in study design and duration of observation

Due to differences in the study design together with the differences in the duration of observation, it cannot be concluded that the ADAPT study is sufficiently similar to the CHAMPION and REGAIN studies for a respective indirect comparison.

The differences in the study design are mainly due to the different treatment strategies. In the ADAPT study, treatment with the study medication was carried out cyclically at different patient-individual intervals. The focus of the study planning was therefore on the assessment of the response at the end of a cycle compared to the beginning of the cycle and not on the assessment of the response primarily at the end of the study (week 26). In contrast, in the REGAIN and CHAMPION studies on the comparative side of the indirect comparison, in which continuous therapy with fixed treatment intervals was carried out, the response at the end of the study was of primary importance. Although it is possible in principle to compare continuous and cyclical patient-individually variable treatment, the ADAPT study was not designed to address such an issue. This is particularly important in the present case because cyclical therapy with efgartigimod alfa is likely to result in a greater fluctuation in response over the course of the study as required than stable, continuous treatment with ravulizumab or eculizumab.

Due to the possibility of early entry into the ADAPT+ extension study (see above), the ADAPT study differs from the studies on the comparator side in the median durations of observation achieved. The median duration of observation in the ADAPT study was only 20 weeks, compared with 26 weeks in the REGAIN and CHAMPION studies. In contrast to the studies on

the comparative side, the majority of patients in the ADAPT study therefore completed the randomised controlled study phase prematurely. In particular, against the background of the different treatment modalities (cyclical vs continuous) and the resulting different responses in the course of the study, the difference of 6 weeks in the median duration of observation does not indicate that there is sufficient similarity between the studies in the two indirect comparisons.

Differences in the patient populations

Irrespective of the differences in study design and the resulting differences in the durations of treatment and observation, both indirect comparisons also show differences between the respective patient populations enrolled.

For the indirect comparison of efgartigimod alfa with eculizumab, the pharmaceutical company used the study population of the REGAIN study, in which subjects with refractory, anti-AChR antibody-positive gMG were enrolled. On the intervention side, the pharmaceutical company formed a sub-population of the ADAPT study based on the inclusion criteria of the REGAIN study. This sub-population should be sufficiently similar to the refractory patient population of the comparator study. However, the criteria used to form the sub-population of the ADAPT study differ from the inclusion criteria of the REGAIN study in particular in that no criteria were applied with regard to the duration of immunosuppressive pretreatment.

The discrepancy with regard to the definition of treatment-refractory patients is reflected, among other things, in the concomitant treatments of the patients enrolled in the studies on the intervention and comparator side. In the REGAIN study, emergency therapy was required more frequently during the course of the study than in the ADAPT study. It can therefore not be concluded that the refractory sub-population of the ADAPT study is sufficiently similar to the study population of the REGAIN study for an indirect comparison.

The indirect comparison of efgartigimod alfa with ravulizumab also shows significant differences between the patients enrolled on the intervention and comparator sides. The CHAMPION study mainly enrolled subjects who were already over 50 years old when the disease occurred (late-onset MG, LOMG). In contrast, the ADAPT study enrolled both subjects with early onset MG (< 50 years, EOMG) and LOMG. There were also differences in the frequency of emergency therapy during the course of the study.

Conclusion

The ADAPT study is not comparable with the CHAMPION and REGAIN studies, which were designed for continuous treatment with fixed dosing intervals and observation of the response at week 26, due to the patient-individual, cyclical treatment regimen combined with the early transfer of patients to the ADAPT+ extension study. In addition, the median duration of observation of the ADAPT study was only 20 weeks. In particular, against the background of the different treatment modalities (cyclical vs continuous) and the resulting different responses in the course of the study, it cannot be concluded from the existing difference in the median durations of observation that there is sufficient similarity between the studies in the two indirect comparisons.

In addition, it cannot be assumed that the patient populations enrolled in the studies on the intervention and comparator sides are sufficiently similar.

In the overall assessment, the indirect comparisons presented by the pharmaceutical company are therefore unsuitable for the assessment of the additional benefit of efgartigimod alfa in comparison with the appropriate comparator therapy. For adults with anti-AChR

antibody-positive gMG who are eligible for an add-on to standard therapy, an additional benefit of efgartigimod alfa is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient efgartigimod alfa due to the exceeding of the € 30 million turnover limit. Efgartigimod alfa has been approved as an orphan drug as an add-on to standard therapy for the treatment of adults with generalised myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive. Eculizumab (only for refractory patients) or ravulizumab was determined as the appropriate comparator therapy.

Due to the absence of any direct comparator studies of efgartigimod alfa versus eculizumab or ravulizumab, the pharmaceutical company presented two adjusted indirect comparisons according to Bucher via the placebo bridge comparator in the dossier. The ADAPT study is presented on the intervention side and the CHAMPION study for ravulizumab and the REGAIN study for eculizumab on the comparator side.

The ADAPT study is not comparable with the CHAMPION and REGAIN studies due to the patient-individual, cyclical treatment regimen combined with the early transfer of patients to the ADAPT+ extension study. The latter were designed for continuous treatment with fixed dosing intervals and observation of the response at week 26.

Early transfer to the ADAPT+ study took place if a new treatment cycle could not be completed within the planned study duration of 26 weeks. As a result, the median duration of observation of the ADAPT study was only 20 weeks. In contrast, the duration of observation on the comparator side was 26 weeks. In particular, against the background of the differences in the study design, i.e. treatment in cycles, and subsequently, a strongly fluctuating response in the course of the ADAPT study compared to continuous treatment in the CHAMPION or REGAIN study, it cannot be concluded from these differences in the median durations of observation that there is sufficient similarity between the studies in the two indirect comparisons.

Furthermore, it cannot be assumed that the patient populations enrolled in the studies on the intervention and comparator sides are sufficiently similar.

In the overall assessment, the indirect comparisons presented by the pharmaceutical company are therefore unsuitable for the assessment of the additional benefit of efgartigimod alfa in comparison with the appropriate comparator therapy. For adults with anti-AChR antibody-positive gMG who are eligible for an add-on to standard therapy, the additional benefit of efgartigimod alfa 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 provided by the pharmaceutical company.

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 present therapeutic indication.

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 Vyvgart (active ingredient: efgartigimod alfa) at the following publicly accessible link (last access: 11 June 2024):

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

Treatment with efgartigimod alfa should only be initiated and monitored by doctors experienced in the therapy of neuromuscular diseases.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 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				
Efgartigimod alfa	1 x every 7 days per 4-week cycle	1 – 7.4	4	4 - 29.6
Appropriate comparator therapy				
Eculizumab (for refractory patients) or ravulizumab				
Eculizumab	Continuously, 1 x every 12-16 days	22.8 - 30.4	1	22.8 - 30.4
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 co-morbidities) 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					
Efgartigimod alfa	1,000 mg	1,000 mg	1 x 1,000 mg	4.0 - 29.6	4.0 - 29.6 x 1,000 mg
Appropriate comparator therapy					
Eculizumab (for refractory patients) or ravulizumab					
Eculizumab	1,200 mg	1,200 mg	4 x 300 mg	22.8 - 30.4	91.2 - 121.6 x 300 mg
Ravulizumab	3,300 mg	3,300 mg	3 x 1,100 mg	6.5	19.5 x 1,100 mg

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

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					
Efgartigimod alfa 1000 mg	1 SFI	€ 17,710.60	€ 2.00	€ 1,008.16	€ 16,700.44
Appropriate comparator therapy					
Eculizumab 300 mg	1 CIS	€ 5,877.85	€ 2.00	€ 335.09	€ 5,540.76
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: 1 September 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 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 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 requirements 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-AChR 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 efgartigimod alfa (Vyvgart); Vyvgart 1,000 mg solution for injection; last revised: May 2024

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 28 November 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 March 2024, the pharmaceutical company submitted a dossier for the benefit assessment of efgartigimod alfa to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 2 April 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 efgartigimod alfa.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 June 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 July 2024. The deadline for submitting statements was 22 July 2024.

The oral hearing was held on 5 August 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 10 September 2024, and the proposed draft resolution was approved.

At its session on 19 September 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 November 2023	Determination of the appropriate comparator therapy
Working group Section 35a	31 July 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 August 2024	Conduct of the oral hearing
Working group Section 35a	14 August 2024 4 September 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	10 June 2024	Concluding discussion of the draft resolution
Plenum	19 September 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 September 2024

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

Prof. Hecken