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
Ravulizumab (New therapeutic indication: myasthenia gravis, anti-AChR antibody-positive)

of 20 April 2023

Contents

Courtesy translation – only the German version is legally binding.

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

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

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

The active ingredient ravulizumab (Ultomiris) was listed for the first time on 1 August 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 21 September 2022, ravulizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 19 October 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient ravulizumab with the new therapeutic

Courtesy translation – only the German version is legally binding.

indication (add-on to standard therapy in adult acetylcholine receptor (AChR) antibody (AB)-positive patients with generalised myasthenia gravis) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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

The G-BA came to a resolution on whether an additional benefit of ravulizumab 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 ravulizumab.

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 Ravulizumab (Ultomiris) according to product information

Ultomiris 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 20.04.2023):

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 ravulizumab as an add-on to standard therapy:

Eculizumab (for refractory patients) or efgartigimod alfa

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

Courtesy translation – only the German version is legally binding.

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

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

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

on 1. In addition to ravulizumab, the active ingredients efgartigimod alfa, azathioprine, pyridostigmine bromide, neostigmine methylsulphate, distigmine bromide and 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 anti-AChR-antibody (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, a resolution on the benefit assessment of efgartigimod alfa according to Section 35a SGB V dated 16.02.2023 is 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 includes five systematic reviews and the additionally presented guideline "International Consensus Guidance for Management of Myasthenia Gravis: 2020 update". In addition, the completely revised German S2k guideline "Diagnostics and

Courtesy translation – only the German version is legally binding.

Therapy of Myasthenic Syndromes"[2] was recently published, to which clinical experts also made significant reference during the written statement procedure.

Recommendations of the above guidelines for patients with Anti-AChR-Ab-positive generalised myasthenia gravis include cholinesterase inhibitors and immunosuppressants (glucocorticoids, azathioprine, mycophenolate mofetil, ciclosporin A, methotrexate and tacrolimus), thymectomy, complement inhibitors (eculizumab, ravulizumab), a neonatal Fc receptor inhibitor (efgartigimod alfa) and 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. Thus, there is a discrepancy between medicinal products approved in the indication and those recommended by the guideline/ used in healthcare. However, according to Annex VI to the AM-RL, 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 updated version of the S2k guideline, treatment decisions are now 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 ravulizumab, 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-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. Efgartigimod alfa, eculizumab and rituximab are named as first-choice active ingredients (in addition to the active ingredient to be assessed, ravulizumab).

As already described, rituximab is not approved for the present therapeutic indication and, according to the assessment of the clinicians involved in the written statement procedure, does not play a significant role in the current German medical treatment situation.

Efgartigimod alfa was identified as having a considerable additional benefit in the resolution of 16 February 2023.

[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 17.02.2023)

Courtesy translation – only the German version is legally binding.

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 ravulizumab.

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-Ab-positive generalised myasthenia gravis. However, it is assumed that patients for whom treatment with ravulizumab is indicated are either ineligible for thymectomy or have already received it.

In the overall assessment, efgartigimod alfa or eculizumab (only for refractory patients) 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 order.

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.

Change of the appropriate comparator therapy

The adjustment of the appropriate comparator therapy and the patient population primarily takes into account the statements of clinical experts and the S2k guideline that has been published in the meantime. Accordingly, standard therapy alone is no longer an option for patients with anti-AChR-Ab-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy. According to the current body of evidence, the formerly defined patient population a) is no longer considered to be the target population of the approved therapeutic indication, as the use of ravulizumab is only considered for patients with anti-AChR-Ab-positive generalised myasthenia gravis who can no longer be adequately treated with standard therapy. An add-on therapy is used in patients with active and highly active generalised myasthenia gravis. Patients who are refractory to therapy are assigned to this patient collective and, according to current recommendations, they no longer constitute a separate patient group.

Accordingly, the target population of the therapeutic indication is adults with anti-acetylcholine receptor antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy.

In the meantime, the active ingredient efgartigimod alfa has also been approved in the present therapeutic indication. Within the framework of the benefit assessment, a considerable

Courtesy translation – only the German version is legally binding.

additional benefit was determined, on the one hand, while the use in clinical care is already recommended on the other.

Overall, it is therefore appropriate to adjust the appropriate comparator therapy at this time.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ravulizumab 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 has submitted the results of the phase 3 CHAMPION study (ALXN1210-MG-306) as well as an indirect comparison based on this study and the REGAIN study (ECU-MG-301) on eculizumab to prove the additional benefit of ravulizumab.

CHAMPION study

The CHAMPION study is a double-blind, randomised controlled trial that compared the efficacy and safety of ravulizumab with placebo, in each case in combination with standard therapy where appropriate, over 26 weeks. The subsequent open-label, single-arm extension phase over up to 2 years is not relevant for the present benefit assessment due to a lack of comparator data.

175 adults with class II, III or IVa/b generalised myasthenia gravis according to the Myasthenia Gravis Foundation of America (MGFA) classification and positive anti-AChR-antibody status at the time of screening were enrolled in the study. At the start of the study, the study participants had to show disease-specific symptoms *(myasthenia gravis - activities of daily living* (MG-ADL) total score ≥ 6 points).

The treatment with ravulizumab in the intervention arm was in accordance with the dosing scheme as specified in the product information. However, the administration of ravulizumab as an add-on to a standard therapy was not prescribed according to the study design. If the patients received treatment with a standard therapy of cholinesterase inhibitors, non-steroidal immunosuppressants (azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus, cyclophosphamide) and/or oral corticosteroids before the start of the study, they had to continue these stably as background therapy in the study. Treatment with rituximab, eculizumab (or other complement inhibitors) and chronic plasmapheresis/ chronic plasma exchange or chronic administration of intravenous immunoglobulins were not allowed. However, the administration of emergency therapy was possible at the discretion of the principal investigator.

Endpoints included disease-specific symptomatology, health-related quality of life and side effects.

The CHAMPION study cannot be used to derive the additional benefit of ravulizumab because the comparison of ravulizumab +/- standard therapy versus placebo +/- standard therapy does not correspond to the currently determined appropriate comparator therapy.

Courtesy translation – only the German version is legally binding.

REGAIN study

The REGAIN study is a randomised, controlled, double-blind, phase 3 study for treatment with 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-Ab-positive generalised myasthenia gravis 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 was required within the last 12 months.

As in the CHAMPION study, patients who received a stable standard therapy before the start of the study had to continue this stably during the study.

Patient-relevant endpoints were assessed in the categories of morbidity, health-related quality of life and side effects.

Indirect comparison

For the comparison of ravulizumab versus eculizumab, the pharmaceutical company presents an indirect comparison of the CHAMPION and REGAIN studies for the sub-population of patients in the therapeutic indication with refractory, anti-AChR-Ab-positive generalised myasthenia gravis via the bridge comparator placebo using *inverse propensity weighting (IPW)* based on patient-individual data.

Analyses on endpoints were only conducted in the morbidity category. The results on side effects were only compared descriptively for both studies. A differentiated assessment of the advantages and disadvantages of ravulizumab in comparison to eculizumab is therefore fundamentally not possible on the basis of the data presented.

Overall, however, the submitted indirect comparison is not used for the benefit assessment, as it cannot be assumed that the patients in the two studies of the indirect comparison are sufficiently similar. In the REGAIN study, the study population included only subjects with refractory generalised myasthenia gravis. In the CHAMPION study, on the contrary, there was no restriction with regard to the refractoriness of the disease and the pharmaceutical company itself deduced in the dossier that the CHAMPION study population includes a relevant number of patients (38%) with non-refractory generalised myasthenia gravis. No data for the sub-population of refractory patients in the CHAMPION study according to the definition in the REGAIN study were submitted in the course of the written statement procedure.

<u>Overall assessment</u>

For the benefit assessment of ravulizumab for the treatment of anti-AChR-Ab-positive adults with generalised myasthenia gravis as an add-on to standard therapy, the results of the phase 3 CHAMPION study, as well as an indirect comparison based on this study and the REGAIN study on eculizumab, were presented.

Courtesy translation – only the German version is legally binding.

The CHAMPION study compared the efficacy and safety of ravulizumab with placebo - in each case in addition to standard therapy, if necessary. Thus, there are no direct comparator data for ravulizumab versus the appropriate comparator therapy adjusted in the present study.

Furthermore, the indirect comparison by means of IPW via the bridge comparator placebo for the comparison of ravulizumab versus eculizumab presented by the pharmaceutical company is unsuitable for deriving the additional benefit for the sub-population of refractory patients, as it cannot be assumed that the study populations are sufficiently similar.

For adults with anti-AChR-Ab-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy, there are therefore no suitable data to assess the additional benefit of ravulizumab compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of ravulizumab finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

Since the appropriate comparator therapy was adapted during the ongoing process, the pharmaceutical company is given the opportunity to submit a new benefit assessment dossier to the G-BA, taking into account the current appropriate comparator therapy. The aim of this assessment is to be able to make statements about the additional benefit of ravulizumab compared to therapy with efgartigimod alfa or eculizumab for adults with anti-AChR-Ab-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy. In addition, revised data on patient numbers can be presented.

For the renewed benefit assessment after the expiry of the deadline, the dossier should present the results of a comparison of ravulizumab with an active ingredient of the appropriate comparator therapy. For this purpose, the G-BA considers a limitation for the resolution until 1 November 2023 to be appropriate.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product with the active ingredient ravulizumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of ravulizumab (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit is considered as being not proven. The possibility that a benefit assessment for the medicinal product with the active ingredient ravulizumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

Courtesy translation – only the German version is legally binding.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient ravulizumab. The therapeutic indication assessed here is as follows: "Ultomiris 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."

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

For the benefit assessment of ravulizumab, the pharmaceutical company submits the results of the phase 3 CHAMPION study, as well as an indirect comparison based on this study and the REGAIN study on eculizumab.

The CHAMPION study compared the efficacy and safety of ravulizumab with placebo - in each case in addition to standard therapy, if necessary. Thus, there are no direct comparator data for ravulizumab versus the appropriate comparator therapy.

Furthermore, the indirect comparison by means of IPW via the bridge comparator placebo for the comparison of ravulizumab versus eculizumab presented by the pharmaceutical company is unsuitable for deriving the additional benefit for the sub-population of refractory patients, as it cannot be assumed that the study populations are sufficiently similar.

For adults with anti-AChR-antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy, there are therefore no suitable data to assess the additional benefit of ravulizumab compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

The validity of the resolution is limited to 1 November 2023.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA based the resolution on the patient numbers for patients with refractory generalised anti-AChR-Ab-positive generalised myasthenia gravis stated by the pharmaceutical company in the dossier as an approximation of the target population of the therapeutic indication. The information is however subject to uncertainties. Especially since it is unclear to what extent patients with high disease activity/ severity are covered by the operationalisation chosen by the pharmaceutical company.

In addition, patients who already received an add-on to the standard therapy and did not show any symptomatology corresponding to the operationalisation were not taken into account in the calculation.

In a recent case on the active ingredient efgartigimod alfa, the resolution of 16 February 2023 was based on a significantly higher number of patients with anti-AChR-Ab-positive generalised myasthenia gravis in SHI (approx. 14,000 - 16,800). These deviations are due to the adjustment of the patient population in the present procedure, taking into account the updated S2k guideline as well as the statements of clinical experts.

Courtesy translation – only the German version is legally binding.

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 Ultomiris (active ingredient: ravulizumab) at the following publicly accessible link (last access: 25 January 2023):

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

Treatment with ravulizumab should only be initiated and monitored by doctors experienced in the therapy of 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. In particular, the training material contains instructions regarding the increased risk of meningococcal infection under ravulizumab.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 April 2023).

Treatment period:

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.

Unlike ravulizumab and efgartigimod alfa, although the active ingredient eculizumab is not explicitly approved as an add-on to standard therapy, it is assumed with reference to the statements of the assessment report of the European regulatory authority (EMA/CHMP/400124/2019) that eculizumab should generally be used as an add-on to standard therapy. This is also supported by corresponding statements in the S2k guideline.

Thus, the costs of standard therapy are incurred equally for the medicinal product under assessment as well as for the active ingredients of the appropriate comparator therapy and are therefore not listed separately.

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.

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ravulizumab	Continuously, 1 x every 56 days	6.5	1	6.5
Appropriate comparator therapy				
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

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) or body surface area (BSA), the average body measurements were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

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					
Ravulizumab	3,300 mg	3,300 mg	3 x 1,100 mg	6.5	19.5 x 1,100 mg
Appropriate comparator therapy					
Eculizumab	1,200 mg	1,200 mg	4 x 300 mg	22.8 - 30.4	91.2 - 121.6 x 300 mg
Efgartigimod alfa	10 mg/kg BW	770 mg	2 x 400 mg	4 - 29.6	8 - 59.2 x 400 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

Courtesy translation – only the German version is legally binding.

the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Ravulizumab 1,100 mg	1 CIS	€ 19,281.15	€ 2.00	€ 786.11	€ 18,493.04
Appropriate comparator therapy					
Eculizumab 300 mg	1 CIS	€ 5,877.85	€ 2.00	€ 574.44	€ 5,301.41
Efgartigimod alfa	1 CIS	€ 9,522.39	€ 2.00	€ 926.63	€ 8,593.76
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 April 2023

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 had 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 drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of

Courtesy translation – only the German version is legally binding.

€ 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Ravulizumab

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

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

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

3. Bureaucratic costs calculation

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

Courtesy translation – only the German version is legally binding.

4. Process sequence

At its session on 9 March 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 5 October 2022.

On 19 October 2022, the pharmaceutical company submitted a dossier for the benefit assessment of ravulizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 21 October 2022 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 ravulizumab.

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

The oral hearing was held on 6 March 2023.

On 12 April 2023, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 12 April 2023 replaces version 1.0 of the dossier assessment dated 30 January 2023. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 11 April 2023, and the proposed resolution was approved.

At its session on 20 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Courtesy translation – only the German version is legally binding.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 March 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	5 October 2022	Change in the appropriate comparator therapy after positive opinion
Working group Section 35a	1 March 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 April 2023	Conduct of the oral hearing
Working group Section 35a	15 March 2023 5 April 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 April 2023	Concluding discussion of the draft resolution
Plenum	20 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 April 2023

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

Prof. Hecken

Courtesy translation – only the German version is legally binding.