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: neuromyelitis optica spectrum disorders, anti-aquaporin-4 IgG seropositive)

of 7 December 2023

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The 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 5 May 2023, 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 2 June 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 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 indication

"Treatment of adults with NMOSD who are anti-aquaporin 4 (AQP4) antibody-positive"

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The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 September 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 in the treatment of adult patients with NMOSD who are anti-aquaporin 4 (AQP4) antibody-positive

Therapeutic indication of the resolution (resolution of 07.12.2023):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive

Appropriate comparator therapy:

Eculizumab (from the 2nd relapse) or satralizumab

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

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

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.

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

on 1. In addition to ravulizumab, the active ingredient eculizumab is approved for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 IgG (AQP4 IgG) positive and show a relapsing disease course. In addition, the active ingredient satralizumab is approved for the treatment of NMOSD in adults and adolescents aged 12 years or older who are anti-AQP4 IgG seropositive. The active ingredient inebilizumab is also approved as a monotherapy for the treatment of adults with NMOSD who are anti-AQP4 IgG seropositive.

on 2. Non-medicinal measures as sole appropriate comparator therapy are not considered in the present therapeutic indication.

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

- Satralizumab (resolution according to Section 35a SGB V of 6 January 2022)
- Inebilizumab (resolution according to Section 35a SGB V of 19 January 2023)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

These guidelines list both approved and unapproved medicinal treatments for NMOSD.

According to the S2k guideline of the German Society of Neurology (DGN), the active ingredients eculizumab and rituximab should be prioritised for long-term NMOSD therapy in adults. The active ingredients azathioprine and mycophenolate mofetil, in contrast, are only recommended for further treatment in stable patients or in the case of contraindications to eculizumab and rituximab and are therefore only of lower significance in long-term NMOSD therapy. The active ingredient tocilizumab has a second-line recommendation only.

The active ingredients azathioprine, mycophenolate mofetil, rituximab and tocilizumab are not approved for the present indication. The active ingredient eculizumab is only approved for NMOSD patients who are anti-aquaporin-4 antibody-positive and show a relapsing disease course. The active ingredient satralizumab is approved for adults and adolescents aged 12 years and older with NMOSD who are anti-aquaporin-4 IgG seropositive. The active ingredient inebilizumab is approved for adults with NMOSD who are anti-aquaporin-4 IgG seropositive.

For satralizumab, a hint for a minor additional benefit was identified in the benefit assessment – by resolution of 6 January 2022. In addition, according to the clinical experts, satralizumab is of considerable significance in clinical practice.

No additional benefit was identified for inebilizumab in the benefit assessment by resolution of 19 January 2023. Due to the lack of additional benefit and the recent marketing authorisation, inebilizumab was therefore not considered when determining the appropriate comparator therapy.

In the overall assessment, the G-BA concludes that for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 IgG (AQP4 IgG) seropositive, the active ingredients eculizumab (from the 2nd relapse onwards) and satralizumab are equally appropriate therapy options.

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 ravulizumab is assessed as follows:

For adults with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 IgG (AQP4 IgG) seropositive, the additional benefit is not proven.

Justification:

For adults with NMOSD who are anti-AQP4 IgG seropositive, there are no direct comparator studies of ravulizumab versus the appropriate comparator therapy.

The pharmaceutical company therefore presents a comparison of individual arms from the ALXN1210-NMO-307 (ravulizumab) and ECU-NMO-301 (eculizumab) studies using the propensity score method for the assessment of the additional benefit of ravulizumab versus eculizumab. In addition, it presents a comparison of ravulizumab with both eculizumab and satralizumab (SAkuraStar and SAkuraSky studies) using a network meta-analysis.

The ALXN1210-NMO-307 study is an ongoing single-arm, external placebo-controlled, open-label study of ravulizumab in adults with NMOSD who are AQP4 antibody seropositive and have had at least 1 relapse in the 12 months prior to enrolment in the study.

The ECU-NMO-301 study is a completed, double-blind, randomised, placebo-controlled study of eculizumab in adults with NMOSD who are AQP4 antibody seropositive and have had at least 2 relapses in the 12 months prior to enrolment in the study or at least 3 relapses within 24 months prior to enrolment in the study with at least 1 relapse in the 12 months prior to enrolment in the study.

The SAkuraSky and SAkuraStar studies are each completed, double-blind, RCTs comparing satralizumab with placebo in adults with NMOSD who are AQP4 antibody seropositive or seronegative and have had at least 2 relapses in the 24 months prior to enrolment in the study, 1 of which was within 12 months prior to enrolment in the study (SAkuraSky) or 1 of which was within 12 months prior to enrolment in the study (SAkuraStar).

Overall, however, the comparisons presented are unsuitable for the benefit assessment of ravulizumab versus the appropriate comparator therapy.

The methodology and approach of the pharmaceutical company in the submitted comparison of individual arms using the propensity score procedure is inadequate. It is unclear whether all patients in the ravulizumab arm considered in the propensity score analyses would have generally been eligible for treatment with eculizumab (lack of positivity). In addition, there are clear differences between the patient populations in the studies analysed by the pharmaceutical company (e.g. higher annual relapse rate in the eculizumab study) due to different inclusion and exclusion criteria. There are relevant shortcomings with regard to the selection of confounders and the presentation of the results. Furthermore, a prepared study protocol including an analysis plan and a pre-defined decision structure for the selection of propensity score procedures is missing. The data presented are therefore not interpretable overall.

The presented evaluations of the network meta-analysis are also unsuitable for the present assessment since the external placebo arm is unsuitable as a bridge comparator. Patients in the external placebo arm had a higher disease burden than those in the ravulizumab arm. The pharmaceutical company's analyses include patient data without taking into account deviations in the baseline patient characteristics of the respective studies. Overall, the results of the network meta-analysis are therefore not interpretable due to the unsuitable comparison of ravulizumab vs external placebo arm.

Overall, no data suitable for the benefit assessment of ravulizumab are available, so an additional benefit is not proven.

2.1.4 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 in the treatment of adult patients with NMOSD who are anti-aquaporin 4 (AQP4) antibody-positive.

The G-BA determined eculizumab (from the 2nd relapse onwards) or satralizumab as the appropriate comparator therapy.

In the absence of direct comparator studies against an active ingredient of the appropriate comparator therapy, the pharmaceutical company presented two indirect comparisons for the benefit assessment: a comparison of individual arms from different studies of ravulizumab and eculizumab using a propensity score procedure and a comparison of ravulizumab with both eculizumab and satralizumab using a network meta-analysis.

In the comparison using the propensity score procedure, the methodology and procedure of the pharmaceutical company is inadequate. The data presented are therefore not interpretable. The presented evaluations of the network meta-analysis are also unsuitable for the assessment of the additional benefit.

In the overall assessment, there are therefore no suitable data of ravulizumab compared with the appropriate comparator therapy. An additional benefit is 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 data is based on the patient numbers from the dossier of the pharmaceutical company which are in a largely plausible range.

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 August 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 a specialist in neurology or a specialist in neurology and psychiatry with experience in the treatment of neuromuscular or neuroinflammatory disorders.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient card). The training material contains, in particular, information and warnings about the risk of infections.

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 November 2023).

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.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Ravulizumab	Continuously, 1x every 56 days	6.5	1	6.5
Appropriate comparator therapy				
Eculizumab or satralizumab				
Eculizumab	Continuously, 1 x every 12-16 days	22.8 - 30.4	1	22.8 - 30.4
Satralizumab	Continuously, 1 x every 28 days	13.0	1	13.0

Consumption:

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

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average body height: 1.72 m; average body weight: 77 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					
Ravulizumab	3,300 mg	3,300 mg	3 x 1,100 mg	6.5	19.5 x 1,100 mg
Appropriate comparator therapy					
Eculizumab or satralizumab					
Eculizumab	1,200 mg	1,200 mg	4 x 300 mg	22.8 - 30.4	91.2 – 121.6 x 300 mg
Satralizumab	120 mg	120 mg	1 x 120 mg	13.0	13.0 x 120 mg

Costs:

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

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Cost (pharmacy discount 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	€ 18,004.15	€ 2.00	€ 1,761.64	€ 16,240.51
Appropriate comparator therapy					
Eculizumab 300 mg	1 CIS	€ 5,586.75	€ 2.00	€ 545.94	€ 5,038.81
Satralizumab 120 mg	3 SFI	€ 26,805.02	€ 2.00	€ 2,618.65	€ 24,184.37
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection					

LAUER-TAXE® last revised: 1 November 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 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 drugs 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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

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

Basic principles of the assessed medicinal product

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

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

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

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

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

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

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

Concomitant active ingredient:

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

Adults with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive

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.

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 10 May 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 23 May 2023.

On 2 June 2023, 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 5 June 2023 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 11 September 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 September 2023. The deadline for submitting statements was 6 October 2023.

The oral hearing was held on 23 October 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 28 November 2023, and the proposed resolution was approved.

At its session on 7 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 May 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	23 May 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	17 October 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	23 October 2023	Conduct of the oral hearing
Working group Section 35a	31.10.2023; 14.11.2023;	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	28 November 2023	Concluding discussion of the draft resolution
Plenum	7 December 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 7 December 2023

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

Prof. Hecken