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)
Ublituximab (relapsing multiple sclerosis)

of 1 August 2024

Contents

1. Legal basis ... 2

2. Key points of the resolution ... 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy ... 3

2.1.1 Approved therapeutic indication of Ublituximab (Briumvi) in accordance with the product information ... 3

2.1.2 Appropriate comparator therapy ... 3

2.1.3 Extent and probability of the additional benefit ... 7

2.1.4 Summary of the assessment ... 13

2.2 Number of patients or demarcation of patient groups eligible for treatment ... 14

2.3 Requirements for a quality-assured application ... 15

2.4 Treatment costs ... 15

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 ... 22

3. Bureaucratic costs calculation ... 26

4. Process sequence ... 26

1. Legal basis

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

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

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

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

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient ublituximab on 1 February 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 26 January 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 May 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 ublituximab compared with the appropriate comparator therapy could be determined on the basis of the dossier of

the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 ublituximab.

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 Ublituximab (Briumvi) in accordance with the product information

Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

Therapeutic indication of the resolution (resolution of 01.08.2024):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

Appropriate comparator therapy for ublituximab:

- Dimethyl fumarate or diroximel fumarate or glatiramer acetate or interferon beta-1a or interferon beta-1b or teriflunomide

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

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

Appropriate comparator therapy for ublituximab:

- A patient-individual therapy taking into account the disease activity and prognosis factors,[2] selecting the following active ingredients:

  Fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod

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 e.g. age, symptomatology at onset, regression of relapses, lesion burden and localisation of lesions, presence of intrathecal immunoglobulin synthesis

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. In addition to ublituximab, the following active ingredients are generally approved for the treatment of relapsing multiple sclerosis (RMS) in adults: Alemtuzumab, azathioprine, cladribine, dimethyl fumarate, diroximel fumarate, fingolimod, glatiramer acetate, glucocorticoids (methylprednisolone as well as prednisolone), (peg-)interferon beta-1a, interferon beta-1b, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, siponimod and teriflunomide.

The marketing authorisations of the individual active ingredients differ in part with regard to the required pretreatment and disease activity.

on 2. A non-medicinal treatment option is not considered as a comparator therapy for the therapeutic indication in question.

on 3. In the multiple sclerosis therapeutic indication, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Fampridine: resolution according to Section 35a SGB V of 2 August 2012
- Teriflunomide: resolution according to Section 35a SGB V of 20 March 2014
- Dimethyl fumarate: resolutions according to Section 35a SGB V of 16 October 2014 and 18 January 2024
- Fingolimod: resolution according to Section 35a SGB V of 1 October 2015 (reassessment after the deadline), 19 May 2016 (new therapeutic indication), 20 June 2019 (new therapeutic indication)
- Cladribine: resolution according to Section 35a SGB V of 17 May 2018
- Ocrelizumab: resolution according to Section 35a SGB V of 2 August 2018
- Extract from Cannabis sativa: resolution according to Section 35a SGB V of 1 November 2018 (reassessment after the deadline)
- Siponimod: resolution according to Section 35a SGB V of 20 August 2020
- Ozanimod: resolution according to Section 35a SGB V of 7 January 2021
- Ponesimod: Resolutions according to Section 35a SGB V of 2 December 2021 and 19 May 2022

Furthermore, there is therapeutic information for natalizumab in the therapeutic indication of multiple sclerosis (Annex IV to the Pharmaceuticals Directive; therapeutic information of 16 October 2009).

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.

Overall, the evidence base in the present therapeutic indication must be regarded as limited. The S2k guideline[3] is particularly relevant for the German healthcare context.

In analogy to the therapy algorithm recommended in the guideline, a distinction is basically made between the patient populations with regard to previous therapy (therapy naive or pretreated) and disease severity. According to the marketing authorisation, pretreated patients without active disease progression are not included in the therapeutic indication to be assessed, which is limited to the presence of active disease.

Glucocorticoids are basically the first-line therapy for acute relapse, but are not recommended for relapse prophylaxis and therefore, do not qualify as an appropriate comparator therapy for any of the patient populations.

Patient group a: Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

The active ingredients dimethyl fumarate, diroximel fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b and teriflunomide are generally recommended for therapy naive patients who show no signs of severe disease progression. In the overall assessment of the body of evidence, these are to be regarded as equally appropriate therapy options for patient group a) and can be considered for the majority of these patients.

Due to their marketing authorisation, azathioprine and mitoxantrone are only indicated for a limited sub-population of the patient population covered by the therapeutic indication and are not determined to be the appropriate comparator therapy, also in view of the insufficient evidence and the restrictive guideline recommendations in this regard.

In summary, the active ingredients dimethyl fumarate, diroximel fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b or teriflunomide are determined as appropriate comparator therapy for adults with relapsing forms of multiple sclerosis who have not yet received any disease-modifying therapy and show no indications of severe disease progression.

Patient group b: Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

3 Hemmer B. et al. Diagnosis and therapy of multiple sclerosis, neuromyelitis optica spectrum disorders and MOG-IgG-associated diseases, S2k guideline, 2023, in: German Society of Neurology (ed.), Guidelines for Diagnosis and Therapy in Neurology.

According to the guideline, the active ingredients alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod are recommended for therapy naive patients with indications of severe disease progression as well as pretreated patients with active disease progression.

With regard to the use of alemtuzumab and cladribine, increasing safety risks have become known in recent years, illustrated, among other things, by the issue of Direct Healthcare Professional Communications ("Rote-Hand-Briefe") (cladribine 2022 with warning of liver damage, alemtuzumab 2020 with warning of cardiovascular and autoimmune diseases). For both active ingredients, use is also limited in time according to the respective marketing authorisation (to a maximum of 4 years for alemtuzumab and 2 years for cladribine) and follows a pulsed treatment strategy for which there is little robust evidence overall. Against this background, the mentioned active ingredients are not determined as part of the appropriate comparator therapy.

According to the guideline recommendations, one of the active ingredients under consideration is selected on a patient-individual basis depending on the disease activity and any prognostic factors (e.g. age, symptomatology at onset, regression of relapses, lesion burden and localisation of lesions, presence of intrathecal immunoglobulin synthesis).

In the overall assessment of the evidence and the above explanations, a patient-individual therapy is determined, taking into account disease activity and prognostic factors, by selecting fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod as appropriate comparator therapy for adults with relapsing forms of multiple sclerosis who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy.

An unchanged continuation of the previous therapy is not considered an appropriate implementation of the appropriate comparator therapy if there is an indication to change the disease-modifying therapy. In addition, the therapeutic information for natalizumab must be taken into account.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

Indication of a minor additional benefit

Justification:

For the benefit assessment, the pharmaceutical company submitted data from the double-blind randomised phase III ULTIMATE I and II studies, which compared ublituximab with teriflunomide.

Adults aged ≥ 18 to ≤ 55 years with relapsing forms of multiple sclerosis were enrolled in the studies. Patients should have active disease defined by the presence of at least 2 relapses in the last 2 years or 1 relapse in the last year and/or at least 1 gadolinium (Gd)-enhancing lesion on magnetic resonance imaging (MRI) at the time of screening.

A total of 549 (ULTIMATE I) and 545 (ULTIMATE II) patients were enrolled. Allocation to the intervention arm (treatment with ublituximab) or the comparator arm (treatment with teriflunomide) was based on 1:1 randomisation. In both studies, the treatment duration was 96 weeks.

In the dossier, the data on the total population of the ULTIMATE I and II studies were presented for the benefit assessment. This was drawn up on the basis of a definition of the target population that does not correspond to the differentiation or definition of patient groups made in the context of the determined appropriate comparator therapy. In the written statement procedure, data were subsequently submitted for a study sub-population relevant to the current appropriate comparator therapy, on which the present benefit assessment is based.

In accordance with patient group a, the relevant study sub-population comprises patients with relapsing forms of multiple sclerosis who have not yet received any disease-modifying therapy and show no indications of severe disease progression. The latter was operationalised by the pharmaceutical company as follows: Patients included in the evaluations must not have a high relapse frequency (no more than 2 relapses in the last 2 years and no more than 1 relapse in the last year at the time of screening) and no high MRI lesion burden (no more than 1 Gd-enhancing lesion or no more than 8 T2 lesions at the start of the study).

A total of 172 (ULTIMATE I) and 183 (ULTIMATE II) patients met these requirements; of these, 97 and 75 were treated with ublituximab and 75 and 93 with teriflunomide.

The results of the meta-analysis of patient-individual data from the ULTIMATE I and II studies presented by the pharmaceutical company were used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

The results for overall mortality are based on the evaluations of the safety survey. Overall, one fatal adverse event (AE) occurred among the patients treated with ublituximab in the ULTIMATE I study.

Morbidity

Confirmed disease relapses

For the endpoint of confirmed disease relapses, operationalised via the annual relapse rate, the meta-analysis shows a statistically significant difference in favour of ublituximab.

There is an effect modification here due to the sex characteristic. While there was no statistically significant difference between the treatment groups for women, there was a statistically significant advantage of ublituximab for men.

Confirmed disability progression (EDSS-based)

For the endpoint of confirmed disability progression, no statistically significant difference was detected between the treatment groups.

Severity grade of disability (Multiple Sclerosis Functional Composite [MSFC])

The MSFC is a measurement instrument to collect the severity of disability in multiple sclerosis. The z-score is calculated as a standardised total value from the results of the Timed 25-Foot Walk (T25-FW) to assess walking ability, the 9-Hole Peg Test (9-HPT) to assess coordination and the Paxed Auditory Serial Addition Test (PASAT-3) to assess cognition.

In addition to data from continuous evaluations of the change from the start of the study to week 96, the pharmaceutical company submitted evaluations of responder analyses of the MSFC z-score that refer to an improvement or deterioration by at least 15% of the individual baseline value. Only the continuous evaluations of the change from the start of the study to week 96 are considered here due to the unclear patient relevance of the respective change in the MSFC-z score in this procedure.

In the meta-analysis, no statistically significant difference was detected between the treatment groups for the MFSC z-score.

Fatigue (Fatigue Impact Scale [FIS])

The FIS is a measurement tool for collecting fatigue-related symptomatology and their impact on the daily lives of patients with multiple sclerosis. The responder analyses submitted by the pharmaceutical company on the percentage of patients with improvement or deterioration by at least 15% of the scale range at week 96 are taken into account since both an improvement and a deterioration of fatigue are possible and patient-relevant in the patients in the present therapeutic indication.

In the meta-analyses of the total score of the FIS, no statistically significant difference was detected between the treatment groups.

Quality of life

Multiple Sclerosis Quality of Life 54 [MSQoL-54]

The MSQoL-54 is a disease-specific measurement instrument for collecting health-related quality of life in patients with multiple sclerosis.

The Physical Health Composite Score (PHCS) and Mental Health Composite Score (MHCS), which summarise physical health and mental health respectively, can be calculated from the values of 12 subscales.

The pharmaceutical company submitted responder analyses on the percentage of patients with improvement or deterioration by at least 15% of the scale range. Taking into account the disease progression in this therapeutic indication and the average baseline values in the mid scale range at the start of the study, it can be assumed that both an improvement and a deterioration in health-related quality of life is possible for the patients enrolled in the study. For this reason, evaluations of both operationalisations are taken into account here.

The meta-analysis of the PHCS summary score shows a statistically significant difference in favour of ublituximab for both improvement and deterioration.

However, there were no statistically significant differences between the treatment groups in the evaluations of the improvement and deterioration of the MHCS summary score.

Side effects

Serious adverse events (SAEs)

In the meta-analytic evaluations of the SAEs, there were no statistically significant differences between the treatment groups.
There was an effect modification due to the sex characteristic. While a statistically significant difference to the disadvantage of ublituximab could be derived for women, there were no statistically significant differences between the treatment groups for men.

Severe AEs and therapy discontinuation due to AEs

The meta-analysis does not show any significant differences between the treatment groups for the endpoints of severe AEs and therapy discontinuation due to AEs.

Specific AEs

Infusion-related reactions (AEs), lymphopenia (severe AEs)

For the endpoints of infusion-related reactions (AEs) and lymphopenia (severe AEs), the meta-analysis showed statistically significant differences between the treatment groups to the disadvantage of ublituximab.

Infections and infestations (SAEs)

For the endpoint of infections and infestations (SAEs), the meta-analysis did not show any statistically significant difference between the treatment groups.

Alopecia (AEs)

For the endpoint of alopecia (AEs), the meta-analysis showed a statistically significant difference between the treatment groups in favour of ublituximab.

Overall assessment

The present benefit assessment is based on the results of the ULTIMATE I and II studies, which compared ublituximab with teriflunomide over a period of 96 weeks.

In the process, the evaluations submitted by the pharmaceutical company in the written statement procedure for the relevant study sub-population, which corresponds to patient group a (adults with relapsing forms of multiple sclerosis who have not yet received any disease-modifying therapy and do not show any indications of severe disease progression), are used for the benefit assessment.

In the studies, one death occurred among patients treated with ublituximab.

In the morbidity category, there was a statistically significant advantage of ublituximab over teriflunomide for the endpoint of confirmed disease relapses, operationalised via the annual relapse rate. In subgroup analyses according to the sex characteristic, this advantage was only confirmed in the group of men, while there was no statistically significant difference in the group of women. There were no statistically significant differences for the endpoints of confirmed disability progression, severity of disability and fatigue.

With regard to quality of life, there were advantages of ublituximab over teriflunomide for the Physical Health Composite Score (PHCS) of the MSQoL-54, whereas there were no statistically significant differences between the treatment groups for the Mental Health Composite Score (PHCS).

With regard to side effects, there were no relevant differences for the benefit assessment for the endpoints of severe AEs and therapy discontinuation due to AEs. There was also no statistically significant difference overall for the endpoint of serious adverse events, although there was a disadvantage of ublituximab for women in terms of effect modification, which was not observed for men.

Among the specific AEs, the disadvantages of ublituximab compared to teriflunomide are evident in infusion-related reactions and lymphopenia; however, there were no statistically significant differences in infections and infestations. Ublituximab showed an advantage over teriflunomide for the endpoint of alopecia.

In the overall assessment, advantages were thus observed for the endpoint of confirmed disease relapses in the morbidity category and for the physical summary score of the MSQoL-54 in the quality of life category. However, the advantages observed were not reflected in

other patient-relevant endpoints such as disability progression or fatigue and are therefore considered to be minor in extent overall.

The observed effect modification for the sex characteristic in the present patient population should be emphasised. Thus, the statistically significant advantage shown in the endpoint of confirmed disease relapses could only be confirmed for men in a subgroup analysis, but not for women. This effect modification was also reflected in the category of side effects in the endpoint of serious adverse events: There was no statistically significant difference for men, whereas a statistically significant disadvantage was observed for women.

Despite this observed effect modification for the sex characteristic in two endpoint categories, a further subdivision of the patient population a to be assessed is not made here, taking into account the medical treatment situation and the assessment of the clinical experts during the written statement procedure. The European regulatory authority also did not make any different therapy recommendations for men and women on the basis of the label-enabling evidence. Therefore, no differentiation is made between women and men in the overall assessment of the additional benefit.

As a result, the G-BA identified a minor additional benefit of ublituximab compared with teriflunomide in adults with relapsing forms of multiple sclerosis who have not yet received any disease-modifying therapy and do not show any indications of severe disease progression.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the meta-analysis of patient-individual data from the double-blind randomised ULTIMATE I and II studies. The risk of bias at study level and endpoint level is rated as low in each case.

However, uncertainties result from the described effect modification by the sex characteristic, which is evident in the endpoint categories of morbidity and side effects.

Further limitations arise in view of the percentage of pretreated patients in the relevant study sub-population: Around 17.5% of patients received pretreatment, predominantly with the active ingredient laquinimod, which is not approved in Europe. Against the background of the present target population (patients who have not yet received any disease-modifying therapy), it can therefore be assumed that the reliability of the data relevant for the benefit assessment is limited.

In the overall assessment, the reliability of data of the results is classified in the "indication" category.

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

The additional benefit is not proven.

Justification:
For adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy, no suitable studies could be identified for a comparison of ublituximab versus the appropriate comparator therapy. In the label-enabling ULTIMATE I and II studies, patients in the

comparator arm received teriflunomide. In accordance with the pharmaceutical company's approach in the dossier, these studies are not considered for the present benefit assessment due to the lack of comparison with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Briumvi with the active ingredient ublituximab.

The therapeutic indication assessed here is as follows:

"Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features."

In this therapeutic indication, the question for the benefit assessment was based on two patient groups.

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

and

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

On patient group a)

The active ingredients dimethyl fumarate, diroximel fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b or teriflunomide are determined as appropriate comparator therapy for this patient group.

For the benefit assessment, the data on the relevant study sub-population of the double-blind randomised ULTIMATE I and II studies, which compared ublituximab with teriflunomide, were subsequently submitted by the pharmaceutical company in the written statement procedure.

No relevant difference for the benefit assessment was found for the endpoint of overall mortality.
In the morbidity category, there was an advantage of ublituximab for the endpoint of confirmed disease relapses; there were no relevant differences for the assessment for the endpoints of confirmed disability progression, severity of disability and fatigue.
With regard to quality of life, there were advantages of ublituximab for the physical summary score of the MSQoL-54.
With regard to side effects, there are no relevant differences for the benefit assessment for the endpoints of severe or serious adverse events and therapy discontinuation due to adverse events.

The observed advantages of ublituximab in the endpoints of confirmed disease relapses and physical summary score of the MSQoL-54 in quality of life were not reflected in other patient-relevant endpoints such as disability progression or fatigue and are therefore considered to be minor in extent.

The evaluations presented show an effect modification according to the sex characteristic: The advantage of ublituximab in the endpoint of confirmed disease relapses is only confirmed

in the subgroup of men, whereas in the subgroup of women, there is a disadvantage in the endpoint of serious adverse events.

Against the background of the effect modification shown and in view of the percentage of pretreated patients in the relevant study sub-population, the reliability of data is classified as an indication.

In summary, an indication of a minor additional benefit of ublituximab compared to teriflunomide was found.

On patient group b)

The appropriate comparator therapy for this patient group is determined to be a patient-individual therapy, taking into account disease activity and prognostic factors, selecting fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod.

In accordance with the pharmaceutical company's approach, no studies that would allow a comparison of ublituximab with the appropriate comparator therapy could be identified.

An additional benefit of ublituximab compared to the appropriate comparator therapy is therefore not proven.

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

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

Overall, the information subsequently submitted by the pharmaceutical company in the written statement procedure is subject to uncertainties, which are due, among other things, to the fact that the sum of the estimated numbers for the two patient groups only covers a percentage of all patients with relapsing forms of multiple sclerosis. This results in a discrepancy in the information on the number of patients in the previous resolutions in the therapeutic indication.

With regard to the upper limits, the resolution is therefore based on the information on the total number of patients with relapsing forms of multiple sclerosis from the resolutions on the benefit assessment according to Section 35a SGB V on ponesimod (from 2 December 2021 and 19 May 2022) and the percentages of patient groups a and b are calculated according to the distribution ratio from the patient numbers subsequently submitted by the pharmaceutical company in the written statement procedure.
It is assumed that the total number of patients in the therapeutic indication cannot exceed 223,000 as the total percentage values of patient groups a and b cannot exceed 100%.
Uncertainties in the shown estimate of the upper limits result from the lack of restriction to the presence of an active disease in the information provided in the resolutions on ponesimod, which may result in an overestimate.

With regard to the lower limits, the resolution is based on the information subsequently submitted by the pharmaceutical company in the written statement procedure.
These are based, among other things, on the determination of prevalence using data from the Federal Social Security Office, analyses of outpatient billing data and data from MS registers.
Limitations result from the lack of restriction to SHI in the estimation of prevalence and uncertainties in the determination of percentage values of RMS.

Furthermore, the lack of a standardised definition of severe disease progression or high disease activity as well as uncertainties in determining the percentage values of missing pretreatment represent limitations of the above-mentioned approach.

Overall, the data on the number of patients is subject to uncertainties.

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 Briumvi (active ingredient: ublituximab) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 01 July 2024):

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

Treatment should be initiated and monitored by specialists in neurology or neurology and psychiatry with experience in the treatment of multiple sclerosis.

For adults with relapsing forms of multiple sclerosis who have not yet received any disease-modifying therapy and do not demonstrate severe disease progression, there is an effect modification for the sex characteristic: The advantage of ublituximab in the endpoint of confirmed disease relapses is only confirmed in the subgroup of men, whereas in the subgroup of women, there is a disadvantage in the endpoint of serious adverse events.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2024).

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.

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.

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.

The (daily) doses recommended in the product information were used as the calculation basis.

Different potencies and dosage information are available for interferon beta-1a and glatiramer acetate. Only the most economical options are presented.

According to the product information, continuation of therapy with natalizumab beyond this period of 2 years should only be considered if a new benefit-risk assessment has been carried out beforehand.

Treatment period:

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ublituximab	Continuously, 1 x every 24 weeks	2.2	1	2.2
Appropriate comparator therapy				
Dimethyl fumarate	Continuously, 2 x daily	365.0	1	365.0
Diroximel fumarate	Continuously, 2 x daily	365.0	1	365.0
Glatiramer acetate	Continuously, 3 x weekly	156.4	1	156.4
Interferon beta-1a	Continuously, 1 x weekly	52.1	1	52.1
Interferon beta-1b	Continuously, every 2 days	182.5	1	182.5
Teriflunomide	Continuously, 1 x daily	365.0	1	365.0

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ublituximab	Continuously, 1 x every 24 weeks	2.2	1	2.2
Appropriate comparator therapy				
A patient-individual therapy taking into account the disease activity and prognosis factors, selecting the following active ingredients:				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Fingolimod	Continuously, 1 x daily	365.0	1	365.0
Natalizumab	Continuously, every 4 weeks	13.0	1	13.0
Ocrelizumab	Continuously, every 6 months	2.0	1	2.0
Ofatumumab	Continuously, 1 x monthly	12.0	1	12.0
Ozanimod	Continuously, 1 x daily	365.0	1	365.0
Ponesimod	Continuously, 1 x daily	365.0	1	365.0

Consumption:

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

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					
Ublituximab	450 mg	1 x 450 mg	3 x 150 mg	2.2	6.6 x 450 mg
Appropriate comparator therapy					
Dimethyl fumarate	240 mg	480 mg	2 x 240 mg	365.0	730.0 x 240 mg
Diroximel fumarate	462 mg	924 mg	4 x 231 mg	365.0	1,460.0 x 231 mg
Glatiramer acetate	40 mg	40 mg	1 x 40 mg	156.4	156.4 x 40 mg
Interferon beta-1a	30 µg	30 µg	1 x 30 µg	52.1	52.1 x 30 µg
Interferon beta-1b	250 µg	250 µg	1 x 250 µg	182.5	182.5 x 250 µg
Teriflunomide	14 mg	14 mg	1 x 14 mg	365.0	365.0 x 14 mg

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

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					
Ublituximab	450 mg	1 x 450 mg	3 x 150 mg	2.2	6.6 x 450 mg
Appropriate comparator therapy					
A patient-individual therapy taking into account the disease activity and prognosis factors, selecting the following active ingredients:					
Fingolimod	0.5 mg	0.5 mg	1 x 0.5 mg	365.0	365.0 x 0.5 mg
Natalizumab	300 mg	300 mg	1 x 300 mg	13.0	13.0 x 300 mg
Ocrelizumab	920 mg	920 mg	1 x 920 mg	2.0	2 x 920 mg
Ofatumumab	20 mg	20 mg	1 x 20 mg	12.0	12.0 x 20 mg
Ozanimod	0.92 mg	0.92 mg	1 x 0.92 mg	365.0	365.0 x 0.92 mg
Ponesimod	20 mg	20 mg	1 x 20 mg	365.0	365.0 x 20 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

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					
Ublituximab 150 mg	3 CIS	€ 12,277.87	€ 2.00	€ 697.90	€ 11,577.97
Appropriate comparator therapy					
A patient-individual therapy taking into account the disease activity and prognosis factors, selecting the following active ingredients:					
Dimethyl fumarate 240 mg	196 ECC	€ 3,194.10	€ 2.00	€ 409.42	€ 2,782.68
Diroximel fumarate 231 mg	360 ECC	€ 2,938.07	€ 2.00	€ 164.50	€ 2,771.57
Glatiramer acetate 40 mg	36 PS	€ 2,732.31	€ 2.00	€ 130.93	€ 2,599.38
Interferon beta-1a 30 µg	12 PEN	€ 5,974.70	€ 2.00	€ 337.92	€ 5,634.78
Interferon beta-1b 250 µg	42 PSS	€ 4,472.02	€ 2.00	€ 216.09	€ 4,253.93
Teriflunomide 14 mg	84 FCT	€ 1,721.51	€ 2.00	€ 81.45	€ 1,638.06
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; ECC = enteric-coated hard capsules; CIS = concentrate for the preparation of an infusion solution; PSI = powder for solution for injection; PSS = powder and solvent for solution for injection					

LAUER-TAXE® last revised: 15 July 2024

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression as well as adults who show active disease progression despite treatment with disease-modifying therapy

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					
Ublituximab 150 mg	3 CIS	€ 12,277.87	€ 2.00	€ 697.90	€ 11,577.97
Appropriate comparator therapy					
A patient-individual therapy taking into account the disease activity and prognosis factors, selecting the following active ingredients:					
Fingolimod 0.5 mg	98 HC	€ 446.60	€ 2.00	€ 20.66	€ 423.94
Natalizumab 300 mg	1 CIS	€ 1,998.88	€ 2.00	€ 110.86	€ 1,886.02
Ocrelizumab 920 mg	1 SFI	€ 12,621.08	€ 2.00	€ 0.00	€ 12,619.08

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
Ofatumumab 20 mg	3 PEN	€ 3,905.37	€ 2.00	€ 219.74	€ 3,683.63
Ozanimod 0.92 mg	98 HC	€ 5,469.17	€ 2.00	€ 309.05	€ 5,158.12
Ponesimod 20 mg	84 FCT	€ 3,735.34	€ 2.00	€ 210.03	€ 3,523.31
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PEN = solution for injection in a pre-filled pen					

LAUER-TAXE® last revised: 15 July 2024

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

The subsequently presented measures are not required for all therapy options of the appropriate comparator therapy. Since there is a regular difference between the medicinal product to be assessed and the appropriate comparator therapy, the costs of additionally required SHI services are presented in the resolution.

To reduce infusion-related reactions, premedication (30 - 60 minutes before each infusion or shortly before each injection) with a corticosteroid and an antihistamine must be administered in accordance with the product information for ublituximab or ocrelizumab. The most economical of the recommended options is shown for each corticosteroid. No further specific information on the antihistamine dosage is given, which is why the necessary costs cannot be quantified.

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	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed: Ublituximab							
Dexamethasone 20 mg[4, 5]	10 TAB	€ 32.42	€ 2.00	€ 0.00	€ 30.42	2.2	€ 10.14[6]
Diphenhydramine	Not calculable						
Appropriate comparator therapy for patient group b)							
Ocrelizumab							
Dexamethasone 20 mg[4, 7]	10 TAB	€ 32.42	€ 2.00	€ 0.00	€ 30.42	2	€ 10.14[6]
Antihistamine	Not calculable						
Abbreviations: PII = powder and solvent for the preparation of a solution for injection or infusion; TAB = tablets							

LAUER-TAXE® last revised: 15 June 2024

Patients who are to receive ublituximab, ocrelizumab or ofatumumab must be tested for the presence of a hepatitis B infection before the respective treatment is initiated.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations[8].

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient
Medicinal product to be assessed				
Ublituximab	HBV screening			
	Hepatitis B surface antigen status (GOP 32781)	1	€ 5.50	€ 5.50
	Hepatitis B HBV antibody status (GOP 32614)	1	€ 5.90	€ 5.90

4 Fixed reimbursement rate
5 According to the product information, 100 mg methylprednisolone or 10 - 20 mg dexamethasone (or equivalent) should be administered, without specifying the dosage form.
6 A shelf life of 3 years is taken into account.
7 According to the product information, 20 mg oral dexamethasone (or equivalent) should be administered.
8 S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011; https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient
Appropriate comparator therapy for patient group b)				
Ocrelizumab or Ofatumumab	HBV screening			
	Hepatitis B surface antigen status (GOP 32781)	1	€ 5.50	€ 5.50
	Hepatitis B HBV antibody status (GOP 32614)	1	€ 5.90	€ 5.90

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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

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

Basic principles of the assessed medicinal product

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

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

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

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

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

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

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

Concomitant active ingredient

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

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

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

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

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

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

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

Designation

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

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

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

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression as well as adults who show active disease progression despite treatment with disease-modifying 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 ublituximab (Briumvi); Briumvi® 150 mg Neuraxpharm; last revised: 02/2024

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 24 October 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 26 January 2024, the pharmaceutical company submitted a dossier for the benefit assessment of ublituximab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 26 January 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient ublituximab.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 April 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2024. The deadline for submitting statements was 23 May 2024.

The oral hearing was held on 10 June 2024.

By letter dated 11 June 2024, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by the IQWiG was submitted to the G-BA on 8 July 2024 and 12 July 2024.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 23 July 2024, and the proposed draft resolution was approved.

At its session on 1 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	**Date**	**Subject of consultation**
Subcommittee Medicinal products	24 October 2023	Determination of the appropriate comparator therapy
Working group Section 35a	4 June 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 June 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 June 2024 3 July 2024 17 July 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 July 2024	Concluding discussion of the draft resolution
Plenum	1 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 August 2024

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

Prof. Hecken