Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ozanimod (Relapsing Remitting Multiple Sclerosis)

of 7 January 2021

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 based on 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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient ozanimod in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 July 2020. 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 10 July 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 October 2020 on the website of the G-BA (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 ozanimod 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 set aside in the benefit assessment of ozanimod.

In the light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at 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 ozanimod (Zeposia) in accordance with the product information

Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.

Therapeutic indication of the resolution (resolution of 7 January 2021):

See therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease who have not previously received disease-modifying therapy or adult patients previously treated with disease-modifying therapy whose disease is not highly active.

- Interferon beta-1a or interferon beta-1b or glatiramer acetate, taking into account the authorisation status

b) Adult patients with relapsing remitting multiple sclerosis (RRMS) with highly active disease in spite of prior treatment with disease-modifying therapy[2].

- Alemtuzumab or fingolimod or natalizumab

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 according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.

[1] General methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

[2] Generally, (pre)-treatment should have lasted a minimum of six months. Depending on relapse frequency and the severity of progression of disability, treatment with disease-modifying therapy of less than six months is permissible, but must be justified.

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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. The following active ingredients are approved in principle for treatment of relapsing remitting multiple sclerosis (RRMS) in adults: alemtuzumab, azathioprine, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, glucocorticoids (methyl prednisolone and prednisolone), interferon beta-1a, interferon beta-1b, mitoxantrone hydrochloride, natalizumab, ocrelizumab, peginterferon beta-1a and teriflunomide.

On 2. A non-medicinal treatment cannot be considered as comparator therapy in the therapeutic indication in question.

On 3. For the therapeutic indication multiple sclerosis, the following resolutions on the benefit assessment of medicinal products with new active ingredients in accordance with 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: Resolution according to Section 35a SGB V of 16 October 2014
- 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

In addition, the following therapy information on medicinal applications in the therapeutic indication multiple sclerosis is available:

- Alemtuzumab: Pharmaceuticals Directive Annex IV; therapy information of 15 September 2016
- Natalizumab: Pharmaceuticals Directive Annex IV; therapy information of 16 October 2009

On 4. The general accepted state of medical knowledge on which the decision of the G-BA is based was illustrated by systematic research for guidelines and reviews of clinical studies in this indication.

Ozanimod is approved for patients with relapsing remitting multiple sclerosis with active disease. A distinction is made between prior treatment (therapy-naive or prior treatment) and disease activity (active, highly active) on the basis of the therapeutic indication and the therapy algorithm stipulated by the product information of the corresponding medicinal products and recommended in the guidelines.

Glucocorticoids are the treatment of choice for acute relapses. However, they are not recommended for relapse prophylaxis and cannot be considered as an appropriate comparator therapy for any of the patient populations.

Because of their marketing authorisation, azathioprine and mitoxantrone are indicated only for a limited sub-population of the patient population covered by the therapeutic indication. Azathioprine is indicated for relapsing multiple sclerosis if immunomodulatory therapy and therapy with beta interferons is not possible or a stable course has been achieved under prior treatment with azathioprine. Mitoxantrone is indicated for the treatment of patients with highly active relapsing forms of multiple sclerosis associated with rapidly developing disability for whom no alternative treatment options exist. Azathioprine and mitoxantrone are not considered to be appropriate comparators for treatment of RRMS, based on their therapeutic indications, evidence and their therapeutic value as reserve preparations.

On a) Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease who have not previously received disease-modifying therapy or adult patients previously treated with disease-modifying therapy whose disease is not highly active.

For this group of patients, the following active ingredients are available in accordance with the marketing authorisation and taking the above-named factors into consideration: cladribine, dimethyl fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b, ocrelizumab, peginterferon beta-1a and teriflunomide.

Treatment of relapsing remitting multiple sclerosis in adults can involve both clinically established active ingredients such as beta-interferons (1a or 1b) or glatiramer acetate as well as newer active substances. Considering all the evidence, beta-interferons and glatiramer acetate should be regarded as therapeutically equally effective.

For the active ingredient interferon beta-1a, various proprietary medicinal products are available with different application routes (Rebif® s.c., Avonex® i.m., Plegridy® (pegylated interferon beta-1a) s.c.), as are different application frequencies. When determining the appropriate comparator therapy, the G-BA usually determines active ingredients independently of the proprietary medicinal products available provided that the therapeutic indication to be evaluated does not give rise to any restrictions (e.g. with regard to certain pharmaceutical forms). In the treatment of relapsing remitting multiple sclerosis, no indication-specific criteria regarding the route of application need to be considered. The available direct evidence to compare the proprietary medicinal products Rebif® (INF-β 1a, s.c.) and Avonex® (INF-β 1a, i.m.) is deemed to indicate that the differences demonstrated in the available studies are insufficiently pronounced to indicate that one medicinal product is generally preferable to the other. For the patient-relevant endpoint “prevention of disability progression”, no difference in favour of one of the preparations has been proven. The efficacy of pegylated interferon-beta has so far only been demonstrated in a comparison to placebo. Data directly comparing pegylated interferon with non-pegylated interferon or efficacy data after switching from non-pegylated interferon are not available according to the product information. Hence, no evidence on the benefit of using a proprietary medicinal product is available.

For the newer active ingredients cladribine dimethyl fumarate and teriflunomide, there are resolutions on the benefit assessment according to Section 35a SGB V. An additional benefit compared to the appropriate comparator therapy (interferon beta-1a or -1b or glatiramer acetate) has not been proven for any of these active ingredients.

Since 2018, a further active ingredient, ocrelizumab, has been available to treat adult patients with relapsing remitting multiple sclerosis with active disease. In the benefit assessment according to Section 35a SGB V, an additional benefit compared with interferon beta-1a was found for ocrelizumab in patients who have not yet received any

disease-modifying therapy or who were pretreated with disease-modifying therapy but whose disease is not highly active based on two direct-comparison studies.

Taking into account the entire body of evidence and the results of the benefit assessment for patients who have not yet received disease-modifying therapy or who have previously been treated with disease-modifying therapy but whose disease is not highly active, the active ingredients interferon beta-1a, interferon beta-1b, glatiramer acetate and ocrelizumab are determined to be equally appropriate therapeutic options.

On b) Adult patients with relapsing remitting multiple sclerosis (RRMS) with highly active disease in spite of prior treatment with disease-modifying therapy[1].

For this group of patients, the following active ingredients are available in accordance with the marketing authorisation and taking the above-named factors into consideration: alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, natalizumab, ocrelizumab, peginterferon beta-1a and teriflunomide.

Alemtuzumab, fingolimod and natalizumab, among others, are approved for disease-modifying monotherapy in adults with highly active relapsing remitting multiple sclerosis despite treatment with a complete and appropriate course of at least one disease-modifying therapy. Recent guidelines recommend the use of these highly active ingredients in patients who have developed a highly active disease course despite previously receiving interferons or glatiramer acetate. In these patients, the active ingredients alemtuzumab, fingolimod and natalizumab are equally appropriate treatment options and are therefore determined as the appropriate comparator therapy for patient population b).

The therapeutic recommendations for natalizumab and alemtuzumab therapy must be complied with. For alemtuzumab in particular, it should be noted that, according to the product information, it can only be employed restrictively and is not generally suitable for all patients.

Change of the appropriate comparator therapy

To date, for patients with highly active disease despite prior treatment with disease-modifying MS therapy it was considered appropriate to switch treatment to either alemtuzumab, fingolimod or natalizumab or to another standard therapy agent. However, it became clear during the written-statement procedure on the benefit assessment of ozanimod that patients who do not respond adequately to standard therapy (interferons or glatiramer acetate) and whose disease is highly active despite receiving disease-modifying therapy should, according to the current state of medical knowledge, no longer be considered as candidates, in most cases, for switching between standard therapies. Instead, these patients are as a rule switched to a more active therapy with alemtuzumab, fingolimod or natalizumab. According to the clinicians participating in the written-statement procedure, this is consistent with the care usually provided to patients at present with RRMS whose disease, despite disease-modifying therapy, is highly active.

For this reason, the G-BA considers it appropriate to change the appropriate comparator therapy at this juncture and to adapt it to the current state of medical knowledge.

Nevertheless, it cannot be ruled out that in individual patients with highly active disease (despite prior treatment), due to the course of their disease to date or to the severity and tendency for relapse, switching between standard therapies may still represent a potential therapeutic option. However, in the absence of a generally accepted definition for “highly active disease”, in particular, and taking into account the written and oral statements, it is impossible to categorise such individual patients into a clear group, and hence they do not constitute a patient population of relevance to the evaluation. Hence, it is the view of the G-BA that it would not be appropriate to determine a comparator therapy separately for those patients who are candidates to switch between standard therapies (interferon beta-1a or interferon beta-1b or glatiramer acetate, taking into account the marketing authorisation).

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

2.1.3 Extent and probability of the additional benefit

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

a) Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease who have not previously received disease-modifying therapy or adult patients previously treated with disease-modifying therapy whose disease is not highly active.

   Indication of a minor additional benefit.

Justification:

To support an assessment of additional benefit for ozanimod over interferon beta-1a to treat adult patients with relapsing remitting multiple sclerosis (RRMS), the pharmaceutical company has presented the RADIANCE B and SUNBEAM studies. Both studies are similar in design, differing only in the duration of treatment.

RADIANCE B and SUNBEAM are randomised, double-blind, active-controlled, parallel-group studies, each comparing ozanimod with interferon beta-1a in patients with RRMS. Both studies included adult patients (18 to 55 years) who had experienced ≥ 1 relapse within the 12 months prior to their inclusion in the study or ≥ 1 relapse within 24 months and ≥ 1 gadolinium (Gd)-enhanced lesion within 12 months prior to inclusion in the study. Patients were eligible if their Expanded Disability Status Scale (EDSS) score was 5.0 or less and they had been diagnosed with RRMS in accordance with the revised 2010 McDonald criteria.

A combined total of 2,666 patients were included in the two studies and these were randomly assigned to treatment with 1 mg ozanimod daily (N = 881), 0.5 mg ozanimod daily (N = 894) or 30 µg interferon beta-1a weekly (N = 891). As the 0.5 mg dosage does not conform with the marketing authorisation, this treatment arm is not relevant for the benefit assessment at hand and will not be further considered in the following analysis. Patients were randomised based on their EDSS score at baseline (≤ 3.5 vs > 3.5) and country.

Patients received 24 months of treatment in the RADIANCE B and at least 12 months of treatment in SUNBEAM, which was extended until the last patient had received 12 months of treatment (a median of approximately 14 months). After the blinded phase of treatment in each study, patients from both studies were given the opportunity to participate voluntarily in an open-label, 1-arm extension study. Both studies had a follow-up phase of 28 days.

The primary endpoint in both studies was the annual relapse rate. Secondary endpoints included endpoints on morbidity, health-related quality of life and adverse events (AEs).

The current benefit assessment is based on the meta-analytical summary of both studies, primarily at month 12. The benefit assessment examined whether differences in effects existed

between the two evaluation times in RADIANCE B. For those endpoints on which data were available, no significant differences were observed between the 12- and 24-month evaluations. However, data were not available for all endpoints. In spite of this, it was assumed that a meta-analytical summary of the results at month 12 would be feasible in the present situation with no significant loss of information. The meta-analysis was planned for the confirmed disease progression endpoint and was conducted as part of the authorisation process.

Relevant patient populations

The relevant patient population includes patients who have not yet received disease-modifying therapy for RRMS and patients who have been pre-treated with disease-modifying therapy whose disease is not highly active. Hence, the relevant population comprises a sub-population of the combined population of RADIANCE B and SUNBEAM. Thus, the benefit assessment draws on data from both studies from patients who had either not been previously treated or not adequately pretreated, or – if they had been adequately pretreated – whose disease was not highly active.

The pharmaceutical company defines patients as having received adequate prior treatment if they have received ≥ 6 months of disease-modifying therapy in the year preceding their inclusion in the study (only the most recent treatment was relevant). High disease activity is operationalised as ≥ 1 qualifying relapse (i.e. a relapse during or up to a maximum of 2 months after receiving adequate prior treatment) in the preceding year or ≥ 1 Gd lesion at baseline despite adequate treatment with disease-modifying therapy. The relevant sub-population was approx. 84% of the total population of both studies.

Based on the available data, no significant differences in the sub-populations are evident between the treatment groups. Moreover, there are no marked differences in patient characteristics between the studies. The patients in the relevant sub-population were on average 35 years old, about two-thirds female and over 99% white in ethnicity. It is noteworthy that more than 90 % of the patients originate from Eastern Europe.

About 85% of patients had an EDSS score of < 4 at baseline and approximately 98% had experienced ≥ 1 relapse in the year prior to entering the study. On average, patients had suffered from the disease for approximately 6 years prior to the start of the study. Approximately 93% of patients had undergone ≥ 1 prior treatment (both disease-modifying and non-disease-modifying). Nevertheless, only about 16% of the patients had received disease-modifying prior treatment.

Extent and probability of the additional benefit

Mortality

No events were recorded for the endpoint overall mortality.

Morbidity

Confirmed disease relapses (EDSS based)

The meta-analysis of annual relapse rates for the confirmed relapses endpoint revealed a statistically significant difference to the benefit of ozanimod compared to interferon beta-1a.

Confirmed disability progression (EDSS based)

The meta-analysis revealed no statistically significant difference between the treatment groups for the confirmed disability progression after 6 months endpoint.

Severity of disability (assessed on the basis of Multiple Sclerosis Functional Composite (MSFC) scores)

As per the manual, MSFC-z scores are calculated on the basis of the results of the Timed 25-Foot Walk (T25-FW) test to assess walking ability, the 9-Hole Peg Test (9-HPT) to assess coordination, and the Paced Auditory Serial Addition Test (PASAT-3) to assess cognition. In the SUNBEAM study, instead of the PASAT-3, the Symbol Digit Modalities Test (SDMT) was used, an alternative, valid and recommended instrument to assess the severity of cognitive impairment.

For the severity of disability endpoint, the meta-analysis revealed no statistically significant difference in MSFC z-scores between the treatment groups.

Visual acuity (Low Contrast Letter Acuity (LCLA))

For the insomnia visual acuity, the meta-analysis revealed no statistically significant difference between the two treatment groups.

Fatigue

No data were available for the fatigue endpoint, as neither study assessed this endpoint.

Quality of life

Disease-specific quality of life (Multiple Sclerosis Quality of Life (MSQoL) 54)

MSQol-54 is based on the Physical Health Composite Score (PHCS) and the Mental Health Composite Score (MHCS). It is calculated on the basis of a covariant analysis of the mean difference of both from the beginning of the study to month 12. The items satisfaction in sexual function and change in health are not taken into account in the composite scores PHCS and MHCS and are presented as supplements.

The meta-analysis reveals a statistically significant difference in PHCS to the benefit of ozanimod compared to interferon beta-1a. However, the 95 % confidence interval (CI) for the standardised mean difference (SMD) is not entirely beyond the irrelevance range [-0.2; 0.2]. Thus it cannot be deduced that the effect is relevant.
For MHCS, no statistically significant difference was revealed between the two treatment arms. The additional results on SF-36 presented by the pharmaceutical company are not drawn on for the current assessment, as SF-36 was not planned to be collected and the information is already reflected in the MSQoL-54 score.

Side effects

SAEs

With regard to SAEs, the meta-analysis revealed no statistically significant difference between the treatment groups.

Specific AEs

For both the infections and infestations endpoint (SOC, AEs) and the psychiatric disorders endpoint (SOC, AEs), the meta-analysis at month 12 revealed no statistically significant difference between the treatment groups.
For the influenza-like illness endpoint (PT, AEs), the meta-analysis at month 12 revealed a statistically significant difference to the benefit of ozanimod.
For the bradycardia endpoint (PT, AEs), the pharmaceutical company submitted no data as the number of events for this endpoint did not meet the frequency criteria to present them.

Discontinuation due to AEs

For the discontinuation due to AEs endpoint, no statistically significant difference was revealed between the treatment groups.

Overall assessment

The benefit assessment was based on the randomised, double-blind and active-controlled studies RADIANCE B and SUNBEAM, each of which assessed ozanimod versus interferon beta-1a in patients with RRMS. The current assessment is based on a meta-analysis of both studies, primarily at month 12. The relevant patient population includes patients who have not yet received disease-modifying therapy for RRMS and patients who have been pre-treated with disease-modifying therapy whose disease is not highly active. This sub-population was approx. 84% of the total population of both studies.

In the morbidity endpoint category, the meta-analysis revealed a statistically significant difference in annual relapses to the benefit of ozanimod compared to interferon beta-1a in the confirmed relapses endpoint.

However, in the endpoints confirmed disability progression (EDSS-based) after 6 months, severity of disability and visual acuity, no statistically significant difference was revealed between the treatment groups. Neither study assessed the fatigue endpoint.

In the health-related quality of life endpoint category, no statistically significant or relevant difference was revealed between the two treatment arms based on the disease-specific quality of life questionnaire MSQoL.

In the adverse events endpoint category, the meta-analysis did not reveal a statistically significant difference between treatment groups for either SAEs or discontinuations due to AEs. In contrast, the analysis of specific AEs revealed a lower detriment for ozanimod compared to interferon beta-1a for the influenza-like illness endpoint.

Hence, in total, a modest beneficial effect was revealed for ozanimod compared to interferon beta-1a in the confirmed disease relapse endpoint. However, the observed benefit in the reduction of relapse rate cannot be used to deduce a further potential effect on the confirmed disability progression endpoint, which can generally only be assessed after a longer follow-up period. In this respect, delaying disease progression is a very important therapeutic goal for treatment of the chronic disease multiple sclerosis. For all further morbidity endpoints as well as for quality of life, no statistically significant differences between ozanimod and interferon beta-1a were revealed. Regarding adverse events, although a specific AE (influenza-like illness) in detail revealed a difference to the benefit of ozanimod, no differences between treatment arms were revealed in overall SAE rates or in therapy discontinuations due to AEs.

The effects of ozanimod are therefore assessed as a moderate and in some cases not insignificant improvement in therapy-relevant benefit compared to the appropriate comparator therapy, while the magnitude of the additional benefit is assessed as low.

Hence, overall, a minor additional benefit of ozanimod compared to treatment with interferon beta-1a has been revealed for patients with RRMS who have not yet received disease-modifying therapy for RRMS and for those who have previously been treated with disease-modifying therapy but whose disease is not highly active.

Reliability of data (probability of additional benefit)

The benefit assessment is based on a meta-analytical evaluation of two directly comparative randomised clinical studies. The risk of bias at the study level is therefore classified as low. Similarly, the risk of bias for the findings at the endpoint level is considered to be low.

Treatment in the RADIANCE B study lasted 24 months, while median treatment in the SUNBEAM study lasted approx. 14 months. Meta-analytical evaluation of the results was primarily conducted on the basis of study data at month 12. For a chronic disease such as

multiple sclerosis, comparative data over a period of 12 months is not considered sufficient to derive reliable findings on disability progression and long-term safety.

Furthermore, another factor that should be taken into account is that, although subjects had suffered from the disease for a median period of about 6 years prior to entering the study, more than 80% of the patients included in both studies had not yet received any disease-modifying therapy on commencing the study. Because some of the patients had thus suffered from the disease for an extended period of time during which a portion of the patients had not received adequate therapy as defined by the current standard of care, the study population can be viewed critically as being poorly representative in the context of the German healthcare system.

Owing to such uncertainties and despite the fact that the two RCTSs are directly comparable, the findings should be categorised as indicating rather than proving an additional benefit.

b) Adult patients with relapsing remitting multiple sclerosis (RRMS) with highly active disease in spite of prior treatment with disease-modifying therapy.

An additional benefit is not proven.

Justification:

To assess the additional benefit of ozanimod, the pharmaceutical company has presented the RADIANCE B and SUNBEAM studies. Both studies compare ozanimod versus interferon beta-1a in adult patients with relapsing remitting multiple sclerosis (RRMS). The relevant patient population comprises patients suffering from highly active RRMS despite receiving treatment with disease-modifying therapy.

However, the appropriate comparator therapy as determined by the G-BA, an escalation to a more active therapy (alemtuzumab, fingolimod, or natalizumab), was not implemented in those patients whose disease was highly active despite receiving prior treatment. Hence, for these patients, no appropriate data are available for a comparison with the appropriate comparator therapy. An additional benefit is therefore not proven.

2.1.4 Limitation of the period of validity of the resolution

b) Adult patients with relapsing remitting multiple sclerosis (RRMS) with highly active disease in spite of prior treatment with disease-modifying therapy.

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

For those patients with RRMS with highly active disease despite having been treated with disease-modifying therapy, the pharmaceutical company has presented data directly comparing ozanimod versus therapy with interferon beta-1a. However, during the written statement process, it became clear that for these patients, switching between standard therapies (interferon beta-1a or interferon beta-1b or glatiramer acetate) was not an appropriate therapeutic option. On the contrary, patients whose disease is highly active despite receiving prior treatment should be switched to alemtuzumab, fingolimod or natalizumab.

Due to the fact that the appropriate comparator therapy was modified during the ongoing procedure, the pharmaceutical company is given the opportunity to submit a new benefit assessment dossier to the G-BA taking into account the current appropriate comparator therapy. The objective of this assessment would be to provide conclusive evidence of the additional benefit of ozanimod versus therapy with alemtuzumab, fingolimod or natalizumab in RRMS patients with highly active disease (despite receiving previous disease-modifying therapy).

The dossier for the new benefit assessment after expiry of the deadline should include the results comparing ozanimod with active ingredients of the appropriate comparator therapy. For patient population b) a limitation of the resolution until 1 July 2021 is considered to be appropriate.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3, number 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment for the medicinal product ozanimod shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of ozanimod (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven. The possibility that a benefit assessment for the medicinal product ozanimod can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Nos. 2 – 4 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Zeposia with the active ingredient ozanimod.

Zeposia is approved for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features. In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease who have not previously received disease-modifying therapy or adult patients previously treated with disease-modifying therapy whose disease is not highly active.
b) Adult patients with relapsing remitting multiple sclerosis (RRMS) with highly active disease in spite of prior treatment with disease-modifying therapy.

On patient population a)

The active ingredients interferon-beta -1a, interferon-beta 1b, and ocrelizumab were determined as appropriate comparator therapy by the G-BA.

For this patient group, the pharmaceutical company has presented a meta-analysis of two RCTs in which ozanimod was compared with interferon beta-1a. The meta-analytical evaluation was primarily conducted on the basis of study data at month 12.

Overall, a modest beneficial effect was revealed for ozanimod compared to interferon beta-1a in the confirmed disease relapse endpoint and for specific AEs in the influenza-like illness endpoint. However, the observed benefit in reduction of relapse rate is not reflected in the confirmed disability progression endpoint. In addition, no advantage was demonstrated for ozanimod over interferon beta-1a in either quality of life or in the total rate of SAEs.

Due to uncertainties regarding how representative the study population is in the German health care context and regarding the analysis of the data at month 12, the reliability of the results is considered to indicative of an additional benefit.

In the overall view, an indication of a minor additional benefit of ozanimod compared to interferon beta-1a has been established.

On patient population b)

The G-BA determined alemtuzumab, fingolimod or natalizumab to constitute the appropriate comparator therapy.

For this patient group, the pharmaceutical company has presented a meta-analysis of two RCTs in which ozanimod was compared with interferon beta-1a. The meta-analytical evaluation was primarily conducted on the basis of study data at month 12.

However, the appropriate comparator therapy as determined by the G-BA, an escalation to a more active therapy (alemtuzumab, fingolimod, or natalizumab), was not implemented in those patients whose disease was highly active despite receiving prior treatment.

Hence, for these patients, no appropriate data are available for a comparison with the appropriate comparator therapy. The additional benefit of ozanimod compared with the appropriate comparator therapy is therefore not proven.

For patient population b) the resolution is limited until 1 July 2021.

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 information on patient numbers is based on the resolution from 2018 of the G-BA on ocrelizumab in the therapeutic indication relapsing remitting multiple sclerosis (RMS)[3].

The resolution is therefore not based on the estimate of patient numbers derived by the pharmaceutical company in its dossier. This is associated with uncertainties, and the pharmaceutical company has identified a larger number of patients than those cited in the resolution on ocrelizumab. This appears inconsistent in that fewer patients are covered by the therapeutic indication of ozanimod (RRMS) than that of ocrelizumab (RMS). Accordingly, the current resolution is based on the patient numbers from the resolution on ocrelizumab. However, it should be borne in mind that patient numbers thus derived should still be regarded as an overestimate.

[3] Resolution of 2 August 2018 on ocrelizumab (RMS + PPMS).

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 Zeposia (active ingredient: ozanimod) at the following publicly accessible link (last access: 6 October 2020):

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

Treatment with ozanimod should only be initiated and monitored by specialists in neurology who are experienced in the treatment of multiple sclerosis.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide a check-list for physicians, a guideline for patients and caregivers and a patient reminder card. The training and information material shall include, in particular, instructions on how to deal with the potential side effects of ozanimod and on embryo-foetal toxicity.

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 December 2020).

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”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

For the cost representation, only the dosages of the general case are considered. If the treatment duration is unlimited, initial induction regimens are to be disregarded in the representation of costs. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Different potencies and dosage regimens exist for interferon beta-1a and glatiramer acetate. Only the most cost-effective options are depicted.

Alemtuzumab use is limited to two to four cycles.

According to the product information, after two years, therapy with natalizumab can only be extended after a renewed risk-benefit assessment has been performed.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Ozanimod	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Interferon beta-1a	1 × every 7 days	52.1	1	52.1
Interferon beta-1b	continuously, every 2 days	182.5	1	182.5
Glatiramer acetate	3 × within 7 days	52.1	3	156.4
Ocrelizumab	1 × every 6 months	2	1	2
Patient population b)				
Alemtuzumab	1st year 5 successive days	1	5	5
	2nd year (and 3rd and 4th year if applicable) 3 successive days	1	3	3
Fingolimod	1 × daily	365	1	365
Natalizumab	1 × every 28 days	13	1	13

Usage and consumption:

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					
Ozanimod	0.92 mg	0.92 mg	1 × 0.92 mg	365	365 × 0.92 mg
Appropriate comparator therapy					
Patient population a)					
Interferon beta-1a	30 µg	30 µg	1 × 30 µg	52.1	52.1 × 30 µg
Interferon beta-1b	250 µg	250 µg	1 × 250 µg	182.5	182.5 × 250 µg
Glatiramer acetate	40 mg	40 mg	1 × 40 mg	156.4	156.4 × 40 mg
Ocrelizumab	600 mg	600 mg	2 × 300 mg	2	4 × 300 mg
Patient population b)					
Alemtuzumab	12 mg	12 mg	1 × 12 mg	1st year: 5	1st year: 5 × 12 mg
				2nd year (and 3rd and 4th year if applicable) 3	2nd year (and 3rd and 4th year if applicable) 3 × 12 mg
Fingolimod	0.5 mg	0.5 mg	1 × 0.5 mg	365	365 × 0.5 mg
Natalizumab	300 mg	300 mg	1 × 300 mg	13	13 × 300 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 Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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					
Ozanimod	98 HC	€ 6,954.77	€ 1.77	€ 404.18	€ 6,548.82
Appropriate comparator therapy					
Alemtuzumab	1 CIS	€ 10,878.05	€ 1.77	€ 634.04	€ 10,242.24
Fingolimod	98 HC	€ 5,786.58	€ 1.77	€ 0.00	€ 5,784.81
Glatiramer acetate 40 mg	36 PS	€ 2,663.16	€ 1.77	€ 130.93	€ 2,530.46
Interferon beta-1a 30 µg	4 PEN	€ 1,660.78	€ 1.77	€ 149.08	€ 1,509.93
Interferon beta-1b	42 PSI	€ 4,031.92	€ 1.77	€ 270.08	€ 3,760.07
Natalizumab	1 CIS	€ 2,366.91	€ 1.77	€ 135.39	€ 2,229.75
Ocrelizumab	2 CIS	€ 12,302.64	€ 1.77	€ 0.00	€ 12,300.87
Abbreviations: HC = hard capsules, CIS = concentrate for the preparation of an infusion solution, PS = prefilled syringes, PEN = injection solution in a pre-fabricated pen, PSI = powder and solvent for solution for injection					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 15 December 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

For ocrelizumab, costs for hepatitis B infection testing are regularly incurred. Sensibly coordinated steps are required for the diagnosis[4]. A serological step-by-step diagnostic initially consists of the examination for HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If the HBs antigen is positive, an active HBV infection has been detected.

In order to reduce infusion-related reactions, the following pre-medications must be taken according to the product information of ocrelizumab: 100 mg intravenous methylprednisolone approx. 30 minutes and an antihistamine about 30–60 minutes before each ocrelizumab infusion. The product information does not provide any further details on pre-medication with ozanimod. The costs required for this can therefore not be quantified.

For the active ingredient alemtuzumab, costs are regularly incurred for the investigation of both active and inactive (latent) tuberculosis infections. The costs shown are a blood test (quantitative determination of an *in vitro* interferon-gamma release after *ex vivo* stimulation with antigens specific for mycobacterium tuberculosis-complex (except BCG)). The tuberculin skin test is not mapped because of lack of sensitivity and specificity as well as the possibility of “sensitisation”.

[4] Only if HBs antigen negative and anti-HBc antibody positive.

Designation of the therapy	Description of the service	Number	Costs per unit	Costs per patient per year
Appropriate comparator therapy for patient population a)				
Ocrelizumab	100 mg methyl prednisolone i.v.	2	€ 17.94[5]	€ 35.88
Ocrelizumab	Hbs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[3]	1	€ 89.50	€ 89.50
Appropriate comparator therapy for patient population b)				
Alemtuzumab	Quantitative determination of an *in vitro* interferon-gamma release after *ex vivo* stimulation with antigens (at least ESAT-6 and CFP-10) specific for mycobacterium tuberculosis-complex (except for BCG) (GOP 32670)	1	€ 58.00	€58.00

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances; Sections 4 and 5 Pharmaceutical Price Ordinance) of 1 October 2009 is not fully used to calculate the 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 *Hilfstaxe* in its currently valid version, surcharges for the production of parenteral preparations containing cytostatic agents of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the *Hilfstaxe*. The cost representation is based on the pharmacy sales 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 according to the regulations in Annex 3 of the *Hilfstaxe*.

3. Bureaucratic costs

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.

[5] Costs after deduction of statutory rebates

4. Process sequence

At its session on 7 April 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 10 July 2020, the pharmaceutical company submitted a dossier for the benefit assessment of ozanimod to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 July 2020 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 ozanimod.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 October 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 October 2020. The deadline for submitting written statements was 5 November 2020.

The oral hearing was held on 23 November 2020.

By letter dated 24 November 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 11 December 2020.

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 were discussed at the session of the subcommittee on 22 December 2020, and the proposed resolution was approved.

On 7 January 2021, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	7 April 2020	Determination of the appropriate comparator therapy
Working group Section 35a	18 November 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 November 2020	Conduct of the oral hearing, commissioning of the IQWiG with supplementary assessment of documents
Working group Section 35a	2 December 2020 16 December 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	22 December 2020	Concluding discussion of the draft resolution
Plenum	7 January 2021	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 7 January 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken