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 Siponimod (Secondary Progressive Multiple Sclerosis)

of 20 August 2020

Contents

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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 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 siponimod 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 February 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 4 February 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 May 2020, 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 siponimod 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 assessed 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

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accordance with the General Methods[1] was not used in the benefit assessment of siponimod.

In the light of the above and taking into account the 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 siponimod (Mayzent®) in accordance with the product information

Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity (see section 5.1).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, with ~~flares~~relapses:

- Interferon-beta 1a or interferon-beta 1b or ocrelizumab

b) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, without ~~flares~~relapses:

- Best supportive care

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.
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.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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

On 1. The following medicinal products are generally approved for the treatment of secondary progressive multiple sclerosis, taking into account the information given in the respective product information: Azathioprine, cladribine, glucocorticoids (methylprednisolone and prednisolone), interferon beta-1a, interferon beta-1b, mitoxantrone, and ocrelizumab.

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)

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 generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

Siponimod is approved for the treatment of secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity. A distinction is made between SPMS with and without ~~flares~~relapses on the basis of the therapeutic indication and the therapy algorithm prescribed by the product information of the corresponding medicinal products and recommended in the guidelines.

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

On a) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, with ~~flares~~relapses.

In accordance with the marketing authorisation, the following active ingredients are available for this patient group: Azathioprine, cladribine, interferon beta-1a, interferon beta-1b, mitoxantrone, and ocrelizumab.

For the treatment of SPMS with ~~flares~~relapses in adults, the interferons beta-1a and beta-1b, which have proven themselves in everyday clinical practice, are available in

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addition to newer active ingredients. In the overall view of the evidence, the beta interferons are to be regarded as equally important with regard to their therapeutic use. It should be noted that the proprietary medicinal product Avonex® (interferon beta-1a) is the only beta interferon not approved for SPMS.

For the newer active ingredients cladribine and ocrelizumab, there are resolutions on the benefit assessment according to Section 35a SGB V.
In the early benefit assessment of the active ingredient cladribine, no additional benefit could be derived for patients in the present therapeutic indication. Cladribine is therefore not determined as an appropriate comparator therapy.
Since 2018, the active ingredient ocrelizumab has been available for the treatment of adult patients with relapsing forms of 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 with RMS (RRMS or SPMS with ~~flares~~relapses) 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. For the use of ocrelizumab in SPMS with ~~flares~~relapses, the results of the benefit assessment are accompanied by evidence-based recommendations. Thus, ocrelizumab is also determined as an appropriate comparator therapy.

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 previous therapy 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. Because of the therapeutic indication, evidence, and the therapeutic significance as reserve preparations in the treatment of relapsing-remitting SPMS, azathioprine and mitoxantrone cannot be considered as an appropriate comparator therapy.

In the overall assessment, the active ingredients interferon beta-1a, interferon beta-1b, and ocrelizumab are determined to be equally appropriate therapy options, taking into account the evidence and the results of the benefit assessment for patients with secondary progressive multiple sclerosis and ~~flares~~relapses.

On b) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, without ~~flares~~relapses.

No medicinal products are approved for the therapy situation of SPMS without ~~flares~~relapses. For this reason, best supportive care is named as an appropriate comparator therapy for SPMS without ~~flares~~relapses. Best supportive care is the therapy that ensures the best possible, patient-individual, supportive treatment to alleviate symptoms and improve quality of life. In the German healthcare context, best supportive care for patients with physical disabilities generally also includes non-medicinal therapies such as physiotherapy.

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

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2.1.3 Extent and probability of the additional benefit

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

a) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, with ~~flares~~relapses:

An additional benefit is not proven.

Justification:

The pharmaceutical company does not present any data for the patient population to be evaluated. Thus, no statements on the additional benefit of siponimod compared with the appropriate comparator therapy can be derived. An additional benefit is thus not proven.

b) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, without ~~flares~~relapses:

An additional benefit is not proven.

Justification:

To assess the additional benefit of siponimod compared with BSC for the treatment of adult patients with secondary progressive multiple sclerosis without ~~flares~~relapses, the pharmaceutical company presents the EXPAND study.

The EXPAND study is a randomised, double-blind, placebo-controlled, multi-centre study. The study included adult patients aged 18 to 60 years with SPMS with an Expanded Disability Status Scale (EDSS) value of 3.0 to 6.5. The patients had to have had a previous diagnosis of relapsing-remitting multiple sclerosis (RRMS) in their disease history. The presence of SPMS was defined by disability progression over a period of at least six months. Furthermore, there had to be documented progression in EDSS over a period of two years prior to the start of study (≥ 1 point for EDSS < 6.0 at the start of study, ≥ 0.5 points for EDSS ≥ 6.0 at the start of study), and patients had to have ~~had~~ no ~~flare~~ relapse or corticosteroid treatment within three months prior to randomisation.

At the time of screening, the cytochrome P450 2C9 (CYP2C9) genotype was determined in each patient. In accordance with the requirements in the product information of siponimod, patients with a CYP2C9*3*3 genotype were excluded from participation in the study because these patients metabolise siponimod more slowly.

A total of 1,651 patients were included in the study and randomised to either siponimod treatment (N = 1,105) or placebo (N = 546) at a ratio of 2:1. In addition, all patients received supportive therapies in the sense of best supportive care. Although the study protocol does not contain any concrete guidelines on the use of supportive therapies, all adjunctive medicinal and non-medicinal therapies (e.g. physiotherapy) should be documented.

At the time of the data cut-off of 29 April 2016, the randomised study phase had ended. The randomised study phase should end about three years after the randomisation of the first patient. This results in different observation times for individual patients. For most patients, the study ended more than one year after randomisation. Following the randomised study phase, patients were able to optionally participate in an extension phase in which all patients received siponimod unblinded.

The primary endpoint of the study was disability progression confirmed after three months (assessed by the EDSS). Secondary endpoints include disability progression confirmed after six months, disease ~~flares~~relapses, and the recording of adverse events (AE). In accordance with the study protocol, patients with disability progression during the course of the study confirmed over a period of at least 6 months were able to either continue the blinded

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treatment or discontinue it and, if they remained blinded to the medication they were already on, begin treatment with siponimod or another MS therapy. All endpoints of the study were to be observed until the end of the randomised study phase regardless of whether the patient received the blinded study medication or switched to another MS therapy or siponimod treatment after discontinuation.

Relevant patient population: active SPMS without ~~flares~~relapses

The EXPAND study included patients with SPMS regardless of whether they had disease activity. However, in accordance with the product information, the therapeutic indication of siponimod covers only the treatment of adult patients with SPMS with disease activity as demonstrated by ~~flares~~relapses or imaging of the inflammatory activity. Disease activity detected by imaging is defined as contrast-enhancing T1 lesions or active (new or newly enlarged) T2 lesions. Furthermore, patient population b) includes only patients with SPMS without ~~flares~~relapses.

To select the relevant sub-population (active SPMS without ~~flares~~relapses) from the EXPAND study, the pharmaceutical company defines the following selection criteria: No clinical ~~flare~~ relapse in the two years prior to study inclusion but proven disease activity in imaging (magnetic resonance imaging) in the form of contrast medium (gadolinium) enriching T1 lesions.

Thus, the relevant sub-population for patient population b) includes 128 (11.6%) patients in the siponimod + BSC arm and 61 (11.2%) patients in the placebo + BSC arm of the total population of the EXPAND study. Of these 189 patients, about 75% had received MS therapy that modified the course of the disease before the start of study.

The direct-comparison observation period for the relevant sub-population was 1.8 years (siponimod + BSC) and 1.7 years (placebo + BSC) in median. 87% of patients were observed for more than one year. Fewer than half of the patients were observed for at least two years. Accordingly, no long-term data are available.

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Extent and probability of the additional benefit

Mortality

There are no time-to-event analyses for the overall mortality endpoint. However, in the present situation, a statistically significant difference can be ruled out because of the low proportion of events (one person died in each of the two treatment arms).

Morbidity

Confirmed disability progression (EDSS based)

For the endpoint confirmed disability progression (EDSS-based), the evaluations are used for confirmation over a period of six months. Here, there is no statistically significant difference between the two treatment arms.

Confirmed ~~flare-ups~~disease relapses (EDSS based)

For the endpoint confirmed *disease relapses*~~flare-ups~~, the annual ~~flare~~ relapse rate is regarded as the relevant operationalisation. As confirmation, the EXPAND study evaluated an increase in the EDSS value by ≥ 0.5 points or change by 1 point on two different functional systems or by 2 points on one functional system (except bowel/bladder or cerebral functional system). The annual ~~flare~~ relapse rate shows a statistically significant difference between the two treatment arms to the benefit of siponimod + BSC compared with placebo + BSC.
A statistically significant advantage for siponimod + BSC is also shown for the operationalisation via the period until the first confirmed ~~flare~~ relapse presented additionally.

Severity of disability (MSFC)

For the endpoint severity of disability (measured by the MSFC-z score), there is no statistically significant difference between the two treatment arms at Month 12 compared with the start of study. This result is also reflected in the individual results of the Timed 25-Foot Walk (T25-FW), the 9 Hole Peg Test (9-HPT), and the Paced Auditory Serial Addition Test (PASAT).

Cognitive function (SDMT and BVMT-R)

The cognitive function endpoint was assessed using the Symbol Digit Modalities Test (SDMT) and the Brief Visuospatial Memory Test-Revised (BVMT-R).

For SDMT, at month 12, there was a statistically significant difference in favour of treatment with siponimod compared with the start of study The standardised mean difference in the form of Hedges' g is used to assess the clinical relevance of the result. The 95% confidence interval of the mean difference was not completely outside the irrelevance range of −0.2 to 0.2. Thus, it cannot be concluded with sufficient certainty that the effect is clinically relevant.

For the BVMT-R, there is no statistically significant difference between the two treatment arms at month 12 compared with the start of study.

Vision (LCVA)

For the endpoint vision, surveyed using the LCVA, there was no statistically significant difference between the two treatment arms at month 12 compared with the start of study.

Walking ability (MSWS-12)

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For the endpoint walking ability, measured by MSWS-12, there was no statistically significant difference between the two treatment arms at month 12 compared with the start of study.

Physical function and mental function (each MSIS-29)

For the endpoint physical function (MSIS 29, scales for physical function) as well as for the endpoint mental function (MSIS 29, scales for mental function) there is no statistically significant difference between the two treatment arms at month 12 compared with the start of study.

Health status (EQ-5D VAS)

For the endpoint health status, measured by the VAS of the EQ 5D, there was no statistically significant difference between the two treatment arms at month 12 compared with the start of study.

Quality of life

The endpoint health-related quality of life was not surveyed in the EXPAND study.

Side effects

In the EXPAND study, the endpoints on side effects were to be surveyed until the end of the study regardless of whether patients chose treatment with siponimod or another MS therapy after discontinuation of the blinded treatment. In the benefit assessment, the IQWiG criticised the fact that for the relevant sub-population, only evaluations for the period of blinded treatment with the randomly assigned study medication were submitted and no evaluations for the entire study period.
Furthermore, in the analyses presented on the AE in addition to events that can be clearly assigned to the disease (e.g. “multiple sclerosis relapse”) and events that could be both symptomatology and side effects (e.g. “abdominal pain” and “pain”) were also excluded. The EXPAND study protocol only stipulated that ~~flares~~relapses and disability progression should not be regularly assessed as serious adverse events (SAE). Furthermore, if AE are not included in the safety evaluation for the dossier, a clinically plausible justification must be given with reference to typical symptomatology of the underlying disease. However, this has not been done in the present case. It is therefore possible that a relevant proportion of adverse events were not included in the evaluation of the AE.
Within the framework of the written statement procedure, the pharmaceutical company submitted subsequent evaluations for the relevant patient population in which the entire study period was considered (which the IQWiG had been missing in the benefit assessment). There is still no information available on how events that could be both symptomatology and side effects were dealt with, and no evaluation that does not exclude these events has been provided. Therefore, because of the resulting uncertainty as to whether all safety events were included in the evaluation, the evaluations presented on the AE cannot be assessed with sufficient certainty.

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Overall assessment

The benefit assessment was based on the randomised, double-blind, placebo-controlled EXPAND study, which investigated siponimod + BSC compared with placebo + BSC in adult patients with secondary progressive multiple sclerosis. Patients with SPMS were included in the study regardless of whether they had disease activity. However, the approved therapeutic indication of siponimod covers only SPMS patients with disease activity demonstrated by ~~flares~~relapses or imaging of inflammatory activity. Patient population b) also includes only patients with SPMS and active disease who do not have any ~~flares~~relapses. Retrospectively, those patients who had no clinical ~~flare~~ relapse two years prior to study inclusion but who had proven disease activity in imaging (magnetic resonance imaging) in the form of contrast-enhancing T1 lesions (gadolinium) were assigned to patient population b). These patients represent a small sub-population of the EXPAND study. The evaluation of patient population b) thus included only 11.6% of the patients of the intervention arm (128 patients) and 11.2% of the patients of the comparator arm (61 patients).

In the endpoint category morbidity, there are no statistically significant differences between the two treatment arms in the endpoints on disability progression and severity of the disability. This result is also reflected in the endpoints cognitive function, vision, walking ability, and physical and mental function as well as health status in which no relevant benefit for siponimod was found.
However, a statistically significant advantage in favour of siponimod is shown in the endpoint of confirmed disease ~~flares~~relapses.

The pharmaceutical company did not collect any data in the endpoint category of health-related quality of life.

In the endpoint category of side effects, the pharmaceutical company did not submit evaluable data for the relevant patient population. The side effect profile of siponimod compared with BSC therefore cannot be assessed.

In the foreground of secondary progressive multiple sclerosis is the progressive course of the disease, which is particularly expressed in the disability progression. The primary therapeutic goal of SPMS is therefore to stop disease progression. However, especially in the endpoint of disability progression, no statistically significant benefit was shown for siponimod.
Because of the clinical manifestation of SPMS, relapse prevention is generally not a priority in the treatment of SPMS. This can also be seen from the fact that the patients included in the evaluation have had no ~~flares~~relapses for at least two years before the start of study and that only a few patients (approx. 13%) experienced any ~~flares~~relapses during the course of the study. Although ~~flares~~relapses can continue to occur in the disease stage of SPMS and are associated with limitations for patients, they do not contribute significantly to the long-term disease progression. This is also evident from the results of the sub-population of the EXPAND study because the advantage in favour of siponimod in reducing the annual ~~flare~~ relapse rate is not reflected in disability progression or severity of disability.

In addition, the previous therapy of SPMS patients presents a possible uncertainty regarding the potential effect of siponimod on the reduction of the ~~flare~~ relapse rate. Of the189 patients included in the evaluation of the patient population b), about 75% had received an MS therapy that modifies the course of the disease before the start of study. Sub-group analyses of this characteristic show that the ~~flares~~relapses observed in the EXPAND study occurred almost exclusively in patients who had received MS therapy that modified the course of the disease before the start of study (DMT pre-treatment). This may suggest that the ~~flares~~relapses observed in the course of the study are those that were successfully suppressed by previous MS therapy.
Within the framework of the written statement procedure ~~The~~ the pharmaceutical company also submitted subgroup analyses on the feature discontinuation of DMT pre-treatment (> 12

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months vs ≤ 12 months before start of study) for the endpoint of confirmed ~~flares~~relapses ~~within the framework of the written statement procedure~~. These analyses show that the relative proportion of patients with a disease ~~flare~~ relapse during the course of the study in the group of patients who had not received disease-modifying MS therapy at ≤ 12 months before the start of study, is almost twice as high (approx. 18%) as the relative proportion of approx. 10% in the group of patients who had not received disease-modifying MS therapy for more than 12 months before the start of study. The subsequent subgroup analyses therefore support the assumption that the ~~flares~~relapses observed in the course of the study were particularly those that had been successfully suppressed by previous MS therapy.

Overall, no statistically significant benefit for siponimod was shown for the primary therapeutic goal of SPMS in the endpoint confirmed disability progression. The potential effect of siponimod on the reduction of the ~~flare~~ relapse rate cannot be conclusively assessed because of the insufficient data regarding the influence of previous disease-modifying MS therapies on the ~~flares~~relapses that occurred during the course of the study. Moreover, there are no assessable data on the side effect profile of siponimod.

Thus, in the overall view, an additional benefit of siponimod compared with BSC is not proven.

2.1.4 Summary of the assessment

This assessment refers to the benefit assessment of the new medicinal product Mayzent® with the active ingredient siponimod.
Siponimod is approved for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

In the therapeutic indication to be assessed, two patient populations were distinguished:

a) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, with ~~flares~~relapses.

b) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, without ~~flares~~relapses.

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On patient group a):

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

For this patient group, the pharmaceutical company does not present any data. Thus, no statements can be derived regarding the additional benefit of siponimod compared with the appropriate comparator therapy. An additional benefit is thus not proven.

On patient group b):

Best supportive care was determined as an appropriate comparator therapy by the G-BA.

For this patient group the pharmaceutical company presents the EXPAND RCT in which siponimod + BSC was compared with placebo + BSC in adult patients with secondary progressive multiple sclerosis. The study included patients with SPMS regardless of whether they had disease activity or ~~flares~~relapses. The evaluation of patient population b) thus included only 11.6% of the patients of the intervention arm (128 patients) and 11.2% of the patients of the comparator arm (61 patients). Approx. 75% of patients in this sub-population had received a disease-modifying MS therapy ~~that modifies the course of the disease~~ before the start of study.

In the endpoint category morbidity, there are no statistically significant differences between the two treatment arms in the endpoints on disability progression and severity of ~~the~~ disability. This result is also reflected in the endpoints cognitive function, vision, walking ability, and physical and mental function as well as health status in which no relevant benefit for siponimod was found.
However, a statistically significant advantage in favour of siponimod is shown in the endpoint of confirmed disease ~~flares~~relapses.
While no data were collected for the endpoint category of health-related quality of life, no assessable data were submitted for the endpoint category of side effects.

Overall, no statistically significant benefit for siponimod was shown for the primary therapeutic goal of SPMS in the endpoint confirmed disability progression. The potential effect of siponimod on the reduction of the ~~flare~~ relapse rate cannot be conclusively assessed because of insufficient data regarding the influence of previous disease-modifying MS therapies on the ~~flares~~relapses that occurred during the course of the study. Moreover, there are no assessable data on the side effect profile of siponimod.

Thus, in the overall view, an additional benefit of siponimod compared with BSC is not proven.

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

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

The G-BA bases the resolution on the estimate of the patient numbers derived by the pharmaceutical company in the dossier. Overall, the patient numbers stated by the pharmaceutical company are subject to uncertainties. These are based, in particular, on the uncertain determination of shares for SPMS, disease activity, and ~~flare~~ relapse activity.

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 Mayzent® (active ingredient: siponimod) at the following publicly accessible link (last access: 4 June 2020):
https://www.ema.europa.eu/documents/product-information/mayzent-epar-product-information_de.pdf

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

Before starting treatment with siponimod, patients must undergo CYP2C9 genotyping to determine their CYP2C9 metabolism status. Siponimod should not be used in patients with a CYP2C9*3*3 genotype. In these patients, the use of siponimod leads to significantly increased plasma levels of the active ingredient. In patients with a CYP2C9*2*3 or -*1*3 genotype, the recommended maintenance dose is 1 mg once daily. In all patients with a different CYP2C9 genotype, the recommended maintenance dose of siponimod is 2 mg.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide all doctors who intend to prescribe Mayzent® with an updated training package for doctors. This must include a summary of the characteristics of the medicinal product, a check list for doctors, a guide for patients/caregiver, and a pregnancy reminder card for women of childbearing age.

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 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 is patient-individual 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. 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 schemes are not taken into account for the cost representation because this 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.

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According to the product information, siponimod should not be used in patients with a CYP2C9*3*3 genotype. In patients with a CYP2C9*2*3 or -*1*3 genotype, the recommended maintenance dose is 1 mg once daily (four tablets of 0.25 mg). In all patients with a different CYP2C9 genotype, the recommended maintenance dose of siponimod is 2 mg once daily.

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				
Siponimod	continuously, 1 × daily	365	1	365
Patient population b)				
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Patient population a)				
Interferon beta -1a[2]	continuously, 3 × in 7 days	156.4	1	156.4
Interferon beta -1b	continuously, 1 × every 2 days	182.5	1	182.5
Ocrelizumab	1 × every 6 months	2	1	2
Patient population b)				
Best supportive care	different for each individual patient			

[2] Only the proprietary medicinal product Rebif® (interferon beta-1a) is approved for the treatment of secondary progressive multiple sclerosis with ~~flares~~relapses.

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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					
Siponimod	1 mg 2 mg	1 mg 2 mg	4 × 0.25 mg 1 × 2 mg	365	1,460 × 0.25 mg 365 × 2 mg
Patient population b)					
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Patient population a)					
Interferon beta-1a[2]	44 µg	44 µg	1 × 44 µg	156.4	156.4 × 44 µg
Interferon beta-1b	250 µg	250 µg	1 × 250 µg	182.5	182.5 × 250 µg
Ocrelizumab	600 mg	600 mg	2 × 300 mg	2	4 × 300 mg
Patient population b)					
Best supportive care	different for each individual patient				

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 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.

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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					
Siponimod 0.25 mg	84 FCT	€ 1,713.71	€ 1.77	€ 97.13	€ 1614.81
Siponimod 2 mg	98 FCT	€ 7,792.27	€ 1.77	€ 453.25	€ 7,337.25
Appropriate comparator therapy					
Interferon beta-1a[2]	36 PS	€ 5,535.11	€ 1.77	€ 505.10	€ 5,028.24
Interferon beta-1b	45 PSI	€ 4,107.43	€ 1.77	€ 203.46	€ 3,902.20
Ocrelizumab	2 CIS	€ 12,302.64	€ 1.77	€ 0.00	€ 12,300.87
Best supportive care	different for each individual patient				
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; PSI = powder and solvent for solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 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 siponimod, there are regular costs for a genetic test to determine the individual CYP2C9 metabolism status. Before starting treatment with siponimod, patients must be genotyped for the CYP2C9 gene in order to determine their CYP2C9 metabolism status. Patients who are homozygous for CYP2C9*3 (CYP2C9*3*3 genotype: approx. 0.3 to 0.4% of the population) should not be treated with siponimod. In these patients, the use of siponimod leads to significantly increased plasma levels of the active ingredient. To prevent increased exposure to siponimod, the recommended maintenance dose for patients with a CYP2C9*2*3 genotype (1.4 to 1.7% of the population) or a CYP2C9*1*3 genotype (9 to 12% of the population) is 1 mg daily.

For ocrelizumab, costs for hepatitis B infection testing are regularly incurred. Sensibly coordinated steps are required for the diagnosis[3]. A serological step-by-step diagnostic initially consists of the examination of 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.

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

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In order to reduce infusion-related reactions, the following pre-medications must be taken according to the product information: 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 premedication with an antihistamine. The costs required for this can therefore not be quantified.

Designation of the therapy	Description of the service	Number	Costs per unit	Costs per patient per year
Medicinal product to be assessed				
Siponimod	Genotyping to determine the CYP2C9 metabolic status (GOP 32866)	1	€ 82.00	€ 82.00
Medicinal product to be assessed				
Ocrelizumab	100 mg methyl prednisolone i.v.	2	€ 17.97[4]	€ 35.94
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

[4] Costs after deduction of statutory rebates

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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) is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services in accordance with Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.
According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of 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.

4. Process sequence

At its session on 24 April 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued on 20 November 2019, the appropriate comparator therapy determined by the G-BA was reviewed. At its session on 10 December 2019, the Subcommittee on Medicinal Products adjusted the appropriate comparator therapy accordingly.

On 4 February 2020, the pharmaceutical company submitted a dossier for the benefit assessment of siponimod to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2.

By letter dated 5 February 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 siponimod.

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

The oral hearing was held on 22 June 2020.

By letter dated 23 June 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 16 July 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

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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 28 July 2020, and the proposed resolution was approved.

At its session on 20 August 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	24 April 2019	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	10 December 2019	Adjustment of the appropriate comparator therapy
Working group Section 35a	16 June 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	22 June 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 June 2020 22 July 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 July 2020	Concluding discussion of the draft resolution
Plenum	20 August 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 August 2020

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

Prof. Hecken

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