Gemeinsamer Bundesausschuss

Justification

of 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 Ponesimod (relapsing multiple sclerosis)

of 19 May 2022

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient ponesimod 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 June 2021. 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 14 June 2021.

By resolution of 2 December 2021 (BAnz AT 03.01.2022 B1), the G-BA changed the appropriate comparator therapy for patient population a) and commissioned IQWiG to conduct a new benefit assessment for the proprietary medicinal product Ponvory with the active ingredient ponesimod for patient population a) according to Section 35a paragraph 2 sentence 1 SGB V on the basis of the dossier already submitted by the pharmaceutical company according to Section 35a paragraph 1 sentence 3 SGB V. By the same resolution, the G-BA provisionally

suspended the resolution on the benefit assessment according to Section 35a paragraph 3 sentence 1 SGB V for patient population a) for a period of 6 months.

The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 March 2022, 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 ponesimod compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of ponesimod.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Ponesimod (Ponvory) in accordance with the product information

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

Therapeutic indication of the resolution (resolution of 19 May 2022):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy.

- Interferon beta-1a or interferon beta-1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab, taking into account the marketing authorisation

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

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

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

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

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

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

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

Relapsing multiple sclerosis (RMS) can be divided into two subtypes: relapsing-remitting multiple sclerosis (RRMS) and relapsing secondary progressive multiple sclerosis (rSPMS) with superimposed relapses. Therefore, in the therapeutic indication to be assessed, those medicinal products which are approved for only one of the two subtypes must also be taken into account.

Furthermore, the wordings of the marketing authorisations of the individual active ingredients differ in part with regard to a required pretreatment and the disease activity.

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

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

- Fampridine: resolution according to Section 35a SGB V of 2 August 2012
- Teriflunomide: resolution according to Section 35a SGB V of 20 March 2014 and 20 January 2022 (new therapeutic indication children and adolescents 10 years of age and older)

- 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
- Ozanimod: resolution according to Section 35a SGB V of 7 January 2021
- Ponesimod: resolution according to Section 35a SGB V of 2 December 2021

Furthermore, the following therapeutic information is available for medicinal product applications in the multiple sclerosis therapeutic indication:

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

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.

Ponesimod is approved for adults with relapsing multiple sclerosis and active disease. Relapsing multiple sclerosis (RMS) can be divided into two subtypes: relapsing-remitting multiple sclerosis (RRMS) and relapsing secondary progressive multiple sclerosis (rSPMS) with superimposed relapses. However, the therapeutic indication to be assessed does not explicitly refer to these two subtypes. It is difficult to assign patients to one of the two forms of progression and is usually only possible post-hoc due to the lack of clear criteria and patient characteristics and the smooth transition from RRMS to rSPMS. Therefore, no separate appropriate comparator therapy will be determined for the RRMS and rSPMS subtypes. Instead, the marketing authorisation of the respective active ingredients must be taken into account for the appropriate comparator therapy.

In analogy to the therapy algorithm recommended in guidelines as well as the currently approved therapeutic indications of comparable therapy alternatives, a distinction of the patient populations is basically made with regard to the previous therapy (therapy-naïve or pretreated) and the disease activity (not highly active, highly active).

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

Azathioprine and mitoxantrone are only indicated for a limited sub-population of the patient population covered by the therapeutic indication due to their marketing authorisation. Azathioprine is indicated in relapsing multiple sclerosis when immunomodulatory therapy and therapy with beta interferons are not possible or a stable course has been achieved with previous therapy with azathioprine. Mitoxantrone is indicated for the treatment of patients with highly active, relapsing

multiple sclerosis, associated with rapidly evolving disability, for which no alternative treatment options exist. Azathioprine and mitoxantrone are not considered as appropriate comparator therapy due to their therapeutic indication, evidence and therapeutic significance as reserve preparations in the treatment of RMS.

On a) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy

For this patient group, the following active ingredients are available in accordance with the marketing authorisation and taking into account the previously explained facts: Cladribine, dimethyl fumarate, diroximel fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b, ocrelizumab, ofatumumab, ozanimod, peginterferon beta-1a, ponesimod, siponimod and teriflunomide.

In the overall assessment of the evidence base, beta-interferons and glatiramer acetate are to be regarded as equivalent in terms of their therapeutic use. For the active ingredient interferon beta-1a, proprietary medicinal products are available with different routes of administration (Rebif® s.c.; Avonex® i.m., Plegridy® [pegyliertes Interferon beta-1a] SC / IM) and different frequencies of administration. When determining the appropriate comparator therapy, the G-BA usually determines active ingredients independently of available proprietary medicinal products, provided that no limitations arise due to the therapeutic indication to be assessed (for example, with regard to certain dosage forms). In the treatment of relapsing multiple sclerosis, there are no indication-specific criteria to be considered with regard to a route of administration. The available direct evidence on the comparison of the proprietary medicinal products Rebif® (INF-β 1a, SC) and Avonex® (INF-β 1a, IM) is assessed to the effect that the differences shown in the available studies are not to be assessed to the extent that one medicinal product is to be preferred to the other as a rule. For the patient-relevant endpoint "prevention of disability progression", no difference in favour of one of the preparations could be proven so far. The efficacy of pegylated interferon-beta has so far only been proven in comparison to placebo. Direct comparator data compared to non-pegylated interferon or efficacy data when switching from non-pegylated interferon are not available according to the product information. Thus, there is no evidence regarding an advantage of a proprietary medicinal product.

The active ingredients dimethyl fumarate and teriflunomide are also established in care and are recommended in the guidelines on an equal footing with interferons and glatiramer acetate. However, it should be noted that the use of teriflunomide is restricted in women and men who still wish to have children due to its teratogenic potential.

With ocrelizumab and ozanimod, two further agents are available for the treatment of adults with relapsing-remitting multiple sclerosis with active disease. As part of the benefit assessment according to Section 35a SGB V, an additional benefit was determined for both active ingredients compared to interferon beta-1a in adults who have not yet received disease-modifying therapy or who have been pretreated with disease-modifying therapy but whose disease is not highly active. However, the active ingredient ozanimod has only recently become available as a treatment option for the treatment of relapsing-remitting multiple sclerosis, so that the therapeutic significance cannot yet be conclusively assessed.

The active ingredient siponimod is only approved for the treatment of adults with secondary progressive multiple sclerosis. In the therapeutic indication to be assessed, siponimod would therefore only be considered for patients with relapsing secondary progressive multiple sclerosis (rSPMS) with superimposed relapses according to the marketing authorisation. However, within the framework of the benefit assessment according to Section 35a SGB V, no additional benefit of siponimod compared to interferons or ocrelizumab could be determined for this patient population, so that siponimod is also not seen as an equally appropriate treatment option for this limited patient group.

The active ingredient ofatumumab received marketing authorisation in March 2021 in the indication relapsing multiple sclerosis and has only been available on the German market since September 2021. The active ingredient diroximel fumarate was approved in November 2021 for the treatment of relapsing-remitting multiple sclerosis. For both active ingredients, it is therefore not currently possible to make any statements on the therapeutic significance in the care.

In the overall assessment, taking into account the body of evidence and the results of the benefit assessment for adults who have not yet received disease-modifying therapy or who have been pretreated with disease-modifying therapy but whose disease is not highly active, the active ingredients interferon beta-1a, interferon beta-1b, glatiramer acetate, dimethyl fumarate, teriflunomide and ocrelizumab are determined to be equally appropriate treatment options. The marketing authorisation and product information of the respective medicinal products must be taken into account.

An unchanged continuation of the previous therapy is not considered an appropriate implementation of the appropriate comparator therapy if there is an indication to change the disease-modifying therapy.

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

2.1.3 Extent and probability of the additional benefit

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

a1) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy; EDSS score ≤ 3.5

Indication of a minor additional benefit

a2) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy; EDSS score > 3.5

An additional benefit is not proven.

Justification for patient population a (patient populations a1 and a2):

For the assessment of the additional benefit of ponesimod, the pharmaceutical company presents the randomised, double-blind OPTIMUM study, in which ponesimod was compared to teriflunomide.

Adults with active RMS and a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS) were enrolled in the study. Active disease was defined as the occurrence of ≥ 1 relapse from month 12 to month 1 or ≥ 2 relapses from month 24 to month 1 or ≥ 1 gadolinium (Gd)-enhancing lesion in the last 6 months, each before the first EDSS assessment.

The patients were either not pretreated with disease-modifying therapies or had previously received treatment with interferons, glatiramer acetate, dimethyl fumarate or natalizumab.

A total of 1,133 patients were randomised in the study at a 1:1 ratio to either treatment with ponesimod (N = 567) or treatment with teriflunomide (N = 566).

The treatment with ponesimod and teriflunomide was carried out over a period of 108 weeks, according to the product information. At the end of the blinded treatment phase, patients were able to enter a 1-arm extension study of treatment with ponesimod.

The primary endpoint of the study was the annual relapse rate. Further patient-relevant endpoints were endpoints of the categories morbidity, health-related quality of life and side effects.

Relevant patient population

Patients who had not been pretreated as well as those who had been pretreated with disease-modifying therapy (interferons, glatiramer acetate, natalizumab or dimethyl fumarate) were enrolled in the OPTIMUM study. However, among the pretreated patients were also those whose disease was highly active despite treatment with disease-modifying therapy. This patient collective is not the subject of the patient population a) to be assessed. As the percentage of this patient group in the total study population is low at 7%, the pharmaceutical company only presents the results for the total study population in the dossier. However, a highly active disease can be associated with an increased relapse frequency and subsequently also with an accelerated disability progression, which is why this approach is associated with potential uncertainties in the present case. However, within the framework of the written statement procedure, the pharmaceutical company submitted additional analyses on the relevant sub-population of the OPTIMUM study, in which patients of patient population a) (approx. 93% of the total population) were exclusively enrolled. As the results for this sub-population are almost identical to those of the total population, it is considered justified to conduct the benefit assessment on the basis of the total population of the OPTIMUM study.

Extent and probability of the additional benefit

Mortality

The results on overall mortality are based on the data on lethal AEs. There are no signs of statistically significant differences between the treatment groups.

Morbidity

Confirmed disease relapses (EDSS-based)

For the endpoint of confirmed relapses, operationalised by the annual relapse rate, there is a statistically significant advantage in favour of ponesimod over teriflunomide. There is an effect modification due to the characteristic "EDSS score at the start of the study". While adults with an EDSS score ≤ 3.5 (mild disability) continue to show a statistically significant advantage in favour of ponesimod, adults with an EDSS score > 3.5 (more severe disability) do not show a statistically significant difference between the treatment groups.

Confirmed disability progression (EDSS-based)

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

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

For the endpoint of severity grade of disability, assessed using the MSFC-z score, the pharmaceutical company presents evaluations based on mean differences over the entire course of the study as well as evaluations at week 108. For the present benefit assessment, only evaluations for week 108 are used, which depict the severity grade of disability at the end of treatment.

For the endpoint of severity grade of disability, assessed by the MSFC-z score, there is a statistically significant advantage of ponesimod over teriflunomide. However, the Hedges'g 95% confidence interval is not completely above the irrelevance threshold of 0.20. It does not allow the inference that the effect is clinically relevant.

Fatigue (Patient Global Impression of Severity [PGI-S])

For the endpoint of fatigue, assessed using the PGI-S, the pharmaceutical company presents evaluations based on mean differences over the entire course of the study as well as evaluations for week 108. For the present benefit assessment, evaluations are used exclusively over the entire course of the study, as these also reflect fluctuations over the course of the study.

For the endpoint of fatigue assessed on the basis of the PGI-S, no statistically significant difference was detected between the treatment groups.

Quality of life

Short Form-36 Health Survey Version 2 (SF-36v2)

Health-related quality of life was assessed in the OPTIMUM study using the SF-36v2. The pharmaceutical company submits evaluations of responder analyses related to both an improvement and a deterioration compared to the start of the study. For patients with active RMS, both an improvement and a deterioration of health-related quality of life is possible in the course of the study. In the OPTIMUM study, almost the same number of patients showed an improvement or deterioration in the course of the study. Moreover, the values at the start of the study allow for a development in both directions in a substantial part of the study population. In the present data situation, both operationalisations are therefore taken into account and the results for the assessment of the additional benefit are interpreted in the overall assessment.

For the physical component score (PCS) of the SF-36v2, there is no statistically significant difference between the treatment groups for the evaluations of improvement from the start of the study. For the evaluations of deterioration from the start of the study, there was a statistically significant difference in favour of ponesimod. There is again an effect modification due to the characteristic "EDSS score at start of the study", which is consistent with the effect modification for the endpoint of confirmed disease relapses. While for adults with an EDSS score ≤ 3.5 (mild disability) there is still a statistically significant advantage of ponesimod over teriflunomide, for adults with an EDSS score > 3.5 (more severe disability) there is no statistically significant difference between the treatment groups.

For the mental component score (MCS) of the SF-36v2, there is no statistically significant difference between the treatment groups, neither in terms of improvement nor deterioration compared to the start of the study.

Side effects

SAEs

For the endpoint of SAEs, no statistically significant difference was detected between the treatment groups.

Discontinuation due to AEs

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

Specific AEs

Bradycardia (PT, AE)

For the endpoint of bradycardia, there is a statistically significant difference between the treatment groups to the disadvantage of ponesimod versus teriflunomide.

Infections and infestations (SOC, SAE)

For the endpoint of infections and infestations, no statistically significant difference was detected between the treatment groups.

Alopecia (PT, AE)

For the endpoint of alopecia, there is a statistically significant difference between the treatment groups to the advantage of ponesimod compared to teriflunomide.

Overall assessment

The benefit assessment was based on the OPTIMUM RCT, in which ponesimod was compared with teriflunomide over a period of 108 weeks. The relevant patient population includes adults who have not yet received disease-modifying therapy for active relapsing multiple sclerosis and those who are pretreated with disease-modifying therapy whose disease is not highly active. This sub-population, which is relevant for the present evaluation, comprises a share of approx. 93% of the total study population. Sensitivity analyses show that the results for this sub-population are almost identical to those of the overall population, which is why the results of the total population are used for the benefit assessment.

There was no statistically significant difference between the treatment groups for the endpoint category of mortality.

In the endpoint category of morbidity, there is a statistically significant advantage of ponesimod for the endpoint of confirmed disease relapses, operationalised via the annual relapse rate. There is an effect modification due to the characteristic "EDSS score at the start of the study". While adults with an EDSS score ≤ 3.5 (mild disability) continue to show a statistically significant advantage of ponesimod, adults with an EDSS score > 3.5 (more severe disability) do not show a statistically significant difference between the treatment groups. In the other morbidity endpoints of confirmed disability progression, severity grade of disability and fatigue, there was no statistically significant or relevant difference between the two treatment groups.

In the endpoint category of health-related quality of life, the physical component score (PCS) of the SF-36v2 shows a statistically significant advantage of ponesimod for the evaluations of deterioration from the start of the study. Here, too, there is an effect modification due to the characteristic "EDSS score at the start of the study", which is consistent with the effect modification for the endpoint of confirmed disease relapses. While there is a statistically significant advantage of ponesimod for adults with an EDSS score ≤ 3.5 (mild disability), there is no statistically significant difference between the treatment groups for adults with an EDSS score > 3.5 (more severe disability). For the mental component score (MCS) of the SF-36v2, there is no statistically significant difference between the treatment groups.

In the endpoint category of side effects, there is no statistically significant difference between the treatment groups for the endpoints of SAEs and discontinuation due to AEs. For the specific AEs, a statistically significant difference to the disadvantage of ponesimod compared to teriflunomide is shown in detail for the endpoint of bradycardia and a statistically significant difference to the advantage of ponesimod for the endpoint of alopecia. For the endpoint of infections and infestations, no statistically significant difference was detected between the treatment groups.

In the subgroup analyses for the characteristic "EDSS score at the start of the study" (≤ 3.5 vs > 3.5), different effects were thus shown for the endpoint of confirmed disease relapses and in the physical component score of the SF36v2, depending on the EDSS score of the patients. The effect modifications shown for the characteristic "EDSS score at the start of the study" thus occur consistently in two endpoint categories. The characteristic "EDSS score at the start of the study" was prespecified according to the study protocol and also represented a stratification factor in the randomisation of the study population. Overall, taking this effect

modification into account, it is appropriate to distinguish between two patient groups with regard to the EDSS score when deriving the additional benefit.

In adults with an EDSS score ≤ 3.5 (mild disability), ponesimod showed an advantage over teriflunomide in both morbidity (confirmed disease relapses) and health-related quality of life (SF-36v2, physical component score). However, these observed advantages are not reflected in other patient-relevant endpoints such as disability progression or fatigue. Based on the side effects profile, neither a higher nor a lower harm can be derived for ponesimod overall. The effects of ponesimod in adults with an EDSS score ≤ 3.5 are therefore assessed as a moderate and anything but minor improvement of the therapy-relevant benefit compared to the appropriate comparator therapy, and the extent of the additional benefit is classified as low.

For adults with an EDSS score > 3.5 (more severe disability), there are no statistically significant differences between the treatment groups in the endpoints of mortality, morbidity and health-related quality of life. For the side effects, neither a higher nor a lower harm for ponesimod can be derived for this patient group overall. Overall, the additional benefit of ponesimod compared to teriflunomide in adults with an EDSS score > 3.5 is therefore not proven.

Overall, there is a minor additional benefit of ponesimod over teriflunomide in the treatment of adults with relapsing multiple sclerosis who have not yet received disease-modifying therapy or adults who have received disease-modifying therapy but whose disease is not highly active and who have an EDSS score ≤ 3.5. However, no additional benefit can be derived for ponesimod over teriflunomide in adults with relapsing multiple sclerosis who have not yet received disease-modifying therapy or adults who have been pretreated with disease-modifying therapy and whose disease is not highly active, and who have an EDSS score > 3.5.

Reliability of data (probability of additional benefit)

The benefit assessment is based on the randomised, double-blind OPTIMUM study, which compared ponesimod versus teriflunomide over a period of 108 weeks.

For the endpoint of health-related quality of life, there is a high percentage of missing values (approx. 10% at the start of the study, > 20% by the end of the study), which leads to a high risk of bias of the results for this endpoint.

Furthermore, a high number of protocol deviations occurred in the study overall, which in principle can result in a high risk of bias at the endpoint level. However, the sensitivity analyses on the influence of protocol violations presented in the context of the written statement procedure show that this does not have a relevant influence on the results for the relapse-related endpoints. For the endpoint "bradycardia", the information submitted by the pharmaceutical company still does not allow exclusion of an influence by relevant protocol violations. However, it can be assumed that this would at most strengthen the observed effect to the disadvantage of ponesimod, but not call it into question. Overall, this shows that the reliability of data of the OPTIMUM study is not impaired by the protocol violations.

Overall, one indication is derived for the reliability of data of the OPTIMUM study.

2.1.4 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Ponvory with the active ingredient ponesimod.

Ponesimod is approved for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. In the therapeutic indication under consideration, two patient populations were distinguished, whereby the present assessment exclusively covers patient population a):

a) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy.

   a1) EDSS score ≤ 3.5

   a2) EDSS score > 3.5

b) Adults with relapsing multiple sclerosis (RMS) with highly active disease despite disease-modifying therapy.

On patient population a1)

The G-BA determined interferon beta-1a or interferon beta-1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab as appropriate comparator therapies.

For this patient group, the pharmaceutical company presents the OPTIMUM RCT, in which ponesimod was compared to teriflunomide over a period of 108 weeks.
For adults with an EDSS score ≤ 3.5 (mild disability), there is no statistically significant difference between the treatment groups in the endpoint of mortality. In the morbidity endpoint of confirmed disease relapses as well as in the health-related quality of life in the deterioration of the physical component score of the SF-36v2, a statistically significant advantage is shown in each case. However, these advantages are not reflected in other patient-relevant endpoints such as disability progression or fatigue. Based on the side effects, neither a higher nor a lower harm can be derived for ponesimod overall.

In the overall assessment, therefore, an indication of a minor additional benefit of ponesimod over teriflunomide in adults with an EDSS score ≤ 3.5 is established.

On patient population a2)

The G-BA determined interferon beta-1a or interferon beta-1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab as appropriate comparator therapies.

For this patient group, the pharmaceutical company presents the OPTIMUM RCT, in which ponesimod was compared to teriflunomide over a period of 108 weeks.
For adults with an EDSS score > 3.5 (more severe disability), there are no statistically significant differences between the treatment groups in the endpoint categories of mortality, morbidity and health-related quality of life. Also, on the basis of the side effects, neither a higher nor a lower harm can be derived for ponesimod overall.

In the overall assessment, therefore, no additional benefit of ponesimod over teriflunomide in adults with an EDSS score > 3.5 can be established.

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 its resolution on the estimate of patient numbers derived by the pharmaceutical company in the dossier. Overall, the derivation of patient numbers is comprehensible, but subject to uncertainty. This uncertainty results, in particular, from the fact that there is currently no uniform definition of high disease activity. The use of different selection criteria can therefore result in different percentages.

In addition, the target population of patient population a) was not explicitly restricted to adults with active RMS, which is why the patient numbers for patient population a) are to be regarded as overestimated.

The current figures are higher, compared to the information in the resolution on ocrelizumab in the same therapeutic indication (relapsing multiple sclerosis) from 2018[2]. However, the assumption of higher percentages of RMS seems plausible and is consistent with the current publication Flachenecker et al. (2020) based on percentage data reported by the DMSG MS registry from 2014 to 2018.

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 Ponvory (active ingredient: ponesimod) at the following publicly accessible link (last access: 21 February 2022):

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

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

According to the requirements of the European Medicines Agency (EMA) with regard to additional measures for risk minimisation, the pharmaceutical company must provide healthcare professionals with a checklist for the reduction of medicinal product and application risks as well as a patient guideline and a patient card for safe use.

2 Resolution of 2 August 2018 on ocrelizumab (RMS + PPMS)

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2022).

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", time intervals between individual treatments and for 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 not limited, initial induction schemes are not considered for the cost representation. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ponesimod	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Interferon beta-1a	continuously, 1 x every 7 days	52.1	1	52.1
Interferon beta-1b	continuously, every 2 days	182.5	1	182.5
Glatiramer acetate	continuously, 3 x every 7 days	156.4	1	156.4
Dimethyl fumarate	continuously, 2 x daily	365	1	365
Teriflunomide	continuously, 1 x daily	365	1	365
Ocrelizumab	continuously, 1 x every 6 months	2	1	2

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					
Ponesimod	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Appropriate comparator therapy					
Patient population a)					
Interferon beta-1a	30 µg	30 µg	1 x 30 µg	52.1	52.1 x 30 µg
Interferon beta-1b	250 µg	250 µg	1 x 250 µg	182.5	182.5 x 250 µg
Glatiramer acetate	40 mg	40 mg	1 x 40 mg	156.4	156.4 x 40 mg
Dimethyl fumarate	240 mg	480 mg	2 x 240 mg	365	730 x 240 mg
Teriflunomide	14 mg	14 mg	1 x 14 mg	365	365 x 14 mg
Ocrelizumab	600 mg	600 mg	2 x 300 mg	2	4 x 300 mg

Costs:

Costs of the medicinal products:

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

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Ponesimod 20 mg	28 FCT	€ 1,869.51	€ 1.77	€ 103.48	€ 1,764.26
Appropriate comparator therapy					
Interferon beta-1a 30 µg	4 PEN	€ 1,712.21	€ 1.77	€ 149.83	€ 1,560.61
Interferon beta-1b 250 µg	42 PSI	€ 4,156.82	€ 1.77	€ 271.43	€ 3,883.62
Glatiramer acetate 40 mg	36 PS	€ 2,732.28	€ 1.77	€ 130.93	€ 2,599.58
Dimethyl fumarate	168 ECC	€ 2,748.54	€ 1.77	€ 153.68	€ 2,593.09
Teriflunomide	84 FCT	€ 3,020.76	€ 1.77	€ 0.00	€ 3,018.99
Ocrelizumab	2 CIS	€ 12,621.04	€ 1.77	€ 0.00	€ 12,619.27
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; ECC = enteric-coated hard capsules; CIS = concentrate for the preparation of an infusion solution; PEN = solution for injection in a pre-filled pen; PSI = powder and solvent for solution for injection					

LAUER-TAXE® last revised: 1 May 2022

Costs for additionally required SHI services:

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

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

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

In order to reduce infusion-related reactions, the following premedications must be given according to the ocrelizumab product information: 100 mg intravenous methylprednisolone about 30 minutes and an antihistamine about 30-60 minutes before each ocrelizumab infusion. The product information does not provide any specific information on the premedication with an antihistamine, which is why the necessary costs cannot be quantified.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Appropriate comparator therapy for patient population a)				
Ocrelizumab	100 mg methylprednisolone IV	2	€ 18.70[3]	€ 37.40
	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

3 Costs after deduction of statutory rebates

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies 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 retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 12 January 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 June 2021, the pharmaceutical company submitted a dossier according to Section 35a paragraph 1 sentence 3 SGB V for the benefit assessment of ponesimod to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

In a letter dated 14 June 2021, the G-BA commissioned IQWiG to assess the dossier on the active ingredient ponesimod in accordance with Section 35a paragraph 2 sentence 1 SGB V.

By resolution of 2 December 2021, the G-BA also determined the active ingredient teriflunomide to be a component of the appropriate comparator therapy for patient population a) and commissioned IQWiG to conduct a new benefit assessment for the proprietary medicinal product Ponvory with the active ingredient ponesimod for patient population a) on the basis of the dossier already submitted by the pharmaceutical company. On 2 December 2021, the G-BA provisionally suspended the resolution on the benefit assessment according to Section 35a paragraph 3 sentence 1 SGB V for patient population a) for a period of 6 months.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2022. The deadline for submitting written statements was 22 March 2022.

The oral hearing was held on 11 April 2022.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 May 2022, and the proposed resolution was approved.

At its session on 19 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 January 2021	Determination of the appropriate comparator therapy
Plenum	2 December 2021	Change of the appropriate comparator therapy, temporary suspension of the resolution on the benefit assessment for the patient population a) for a period of 6 months
Working group Section 35a	5 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 April 2022	Conduct of the oral hearing
Working group Section 35a	20 April 2022 3 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	10 May 2022	Concluding discussion of the draft resolution
Plenum	19 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 May 2022

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

Prof. Hecken