Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V – Fingolimod (New Therapeutic Indication: Paediatric Patients with Highly Active Relapsing-remitting Multiple Sclerosis)

From 20 June 2019

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 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 shall pass a resolution 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

On 15 April 2011, the active ingredient Fingolimod was listed for the first time in the “Große Deutsche Spezialitäten-Taxe” (LAUER-TAXE®).

On 22 November 2018, fingolimod for the treatment of paediatric patients with highly active relapsing-remitting multiple sclerosis (RRMS) received marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 number 2a to Regulation (EC) number 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 19 December 2018, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient fingolimod with the new therapeutic indication “for the treatment of paediatric patients with highly active relapsing-remitting multiple sclerosis” in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 01 April 2019, 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 fingolimod 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 and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA 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 fingolimod.

In 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 fingolimod (Gilenya®) in accordance with the summary of product characteristics

Gilenya is indicated as a disease modifying monotherapy in highly active relapsing-remitting multiple sclerosis for the following groups of adult patients and **paediatric patients aged 10 years and older**:

- Patients with highly active relapsing-remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease modifying therapy (see Sections 4.4 and 5.1 for exceptions and information on washout periods).

  or

- Patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy.

This resolution relates exclusively to the newly approved therapeutic indication of 22 November 2018 (i.e. children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis).

[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.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a a full and adequate course with at least one disease modifying therapy for whom escalation of therapy is indicated.

Appropriate comparator therapy:

- Therapy according to the doctor's instructions

a2) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapeutics is indicated.

Appropriate comparator therapy:

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

b1) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received disease modifying therapy.

Appropriate comparator therapy:

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

b2) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy.

Appropriate comparator therapy:

- Therapy according to the doctor's instructions

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 practice unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the efficiency principle.

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, in principle, have a marketing authorisation for the therapeutic indication.
2. If a non-medical treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-drug 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 approved in principle for the treatment of relapsing-remitting multiple sclerosis in children and adolescents: Azathioprine, glatiramer acetate, interferon beta-1a, and interferon beta-1b. The marketing authorisation and summary of product characteristics must be observed.

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

On 3. For the therapeutic indication multiple sclerosis (adult patients), the following resolutions of the G-BA 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 01 October 2015 (revaluation after the deadline), 18 December 2014 (new therapeutic indication), 19 May 2016 (new therapeutic indication)
- Cladribine: Resolution according to Section 35a SGB V of 17 May 2018, 21 June 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 (revaluation after the deadline)

In addition, the following therapy information on drug applications in the therapeutic indication is available:

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

On 4. The generally accepted state of medical knowledge was illustrated by an evidence search and a guideline search.

fingolimod is authorised for the treatment of highly active or rapidly evolving severe relapsing-remitting multiple sclerosis. This includes patients who are therapy-naïve or who have undergone previous treatment.

Interferon beta-1a, interferon beta-1b, and glatiramer acetate are considered as basic therapeutics in the present therapeutic indication, taking into account the authorisation status. If the basic therapeutics used are no longer sufficiently effective, it is possible for children and adolescents with highly active disease to change within the basic therapeutics.

Consequently, for patient groups a2 (Children and adolescents with a highly active disease with at least one disease modifying therapy for whom a change within the basic therapeutics is indicated) and b1 (Children and adolescents with rapidly evolving severe relapsing-remitting multiple sclerosis who have not yet received disease modifying therapy), the active ingredients interferon beta-1a, interferon beta-1b, and glatiramer acetate were identified as equally appropriate comparator therapies, taking into account the authorisation status.

In children and adolescents with highly active or rapidly evolving severe relapsing-remitting multiple sclerosis for whom the basic therapeutic agents are no longer sufficient and for whom escalation of therapy is indicated, there is a discrepancy between medicinal products authorised in the indication and those used in care or recommended in the guidelines: Although the active ingredient natalizumab is not authorised for the present indication, it is recommended for escalation therapy in children and adolescents.

Consequently, for patient groups a1 (Children and adolescents with a highly active disease with at least one disease modifying therapy for whom escalation of therapy is indicated) and b2 (Children and adolescents with rapidly evolving severe relapsing-remitting multiple sclerosis who have already received disease modifying therapy), “therapy according to the doctor’s instructions” was determined as the appropriate comparator therapy. Natalizumab is considered to be a suitable comparator.

Because of the marketing authorisation, azathioprine is indicated only for a restricted sub-population of the patient population covered by the therapeutic indication of fingolimod. Azathioprine is authorised for relapsing-remitting multiple sclerosis when immunomodulatory therapy is indicated and therapy with beta interferons is not possible or a stable course has been achieved under previous therapy with azathioprine. Azathioprine is not an appropriate comparator therapy because of its therapeutic indication, the lack of evidence, and the therapeutic significance as a reserve preparation in the treatment of relapsing-remitting multiple sclerosis.

For the active ingredient interferon beta-1a, proprietary medicinal products are available with different application routes (Rebif® s.c.; Avonex® i.m.) and different application frequencies. When determining the appropriate comparator therapy, the G-BA usually determines active ingredients independently of the proprietary medicinal products available provided that the therapeutic indication to be evaluated does not give rise to any restrictions (e.g. with regard to certain pharmaceutical forms). In the treatment of relapsing-remitting multiple sclerosis, no indication-specific criteria regarding the route of application must be considered. The present direct evidence for adult patients to compare the proprietary medicinal products Rebif® (interferon beta-1a, s.c.) and Avonex® (interferon beta-1a, i.m.) is evaluated in such a way that the differences shown in the present studies are not to be assessed to the extent that one drug is usually preferable to the other. For the patient-relevant endpoint “prevention of disability progression”, no difference in favour of one of the preparations has been proven in adults.

Natalizumab is indicated for the disease modifying monotherapy in adults with highly active relapsing-remitting multiple sclerosis, patients with highly active disease despite treatment with a full and adequate course with at least one disease modifying

therapy, and patients with rapidly evolving relapsing remitting multiple sclerosis. Natalizumab has a long-standing known elevated risk profile for the occurrence of serious adverse events such as the development of progressive multifocal leukoencephalopathy (PML), which can lead to permanent damage or death as well as numerous restrictions imposed by marketing authorisation. Natalizumab is only suitable for patients for whom a change to escalation therapy is the form of therapy in a patient-specific assessment taking into account the overall clinical situation, in particular the severity of the relapses, and which show a high disease activity despite treatment with interferon beta. The potential serious side effects associated with the therapy must be carefully weighed against the severity of the disease and the potential positive effects on the individual patient.

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

2.1.3 Extent and probability of the additional benefit

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

a1) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom escalation of therapy is indicated:

An additional benefit is not proven.

a2) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapeutics is indicated:

Hint for a non-quantifiable additional benefit.

b1) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received disease modifying therapy:

Hint for a non-quantifiable additional benefit.

b2) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy:

An additional benefit is not proven.

Justification:

On patient group a1): (highly-active RRMS, escalation therapy)

No data were submitted for the assessment of the additional benefit of fingolimod over therapy according to the doctor's instructions for the treatment of pretreated children and adolescents with highly active relapsing-remitting multiple sclerosis for whom escalation therapy is indicated. As a result, for this patient group, no conclusions can be drawn about the additional benefit of fingolimod compared to the appropriate comparator therapy.

On patient group a2): (highly active RRMS, change within the basic therapy)

The pharmaceutical company submits the PARADIGMS study for the assessment of the additional benefit of fingolimod over therapy with interferon beta-1a for the treatment of pretreated children and adolescents with highly active relapsing-remitting multiple sclerosis for whom a change within the basic therapeutics is indicated.

The PARADIGMS study is a randomised, double-blind, actively controlled, parallel group study comparing fingolimod with interferon beta-1a (applied i.m.) in paediatric and adolescent patients with RRMS.

Included in the study were children and adolescents (≥ 10 years to < 18 years) who had ≥ 1 relapse in the last year or ≥ 2 relapses in the last 2 years or ≥ 1 Gd lesion within the last 6 months prior to study inclusion and a maximum Expanded Disability Status Scale (EDSS) value of 5.5.

A total of 215 children and adolescents were randomised and assigned to treatment with fingolimod (N = 107) or interferon beta-1a (N = 108). The randomisation was stratified according to region (Eastern, Western Europe, Central and South America, North America, Australia) and pubertal status (pre-pubertal, pubertal). The study duration of the blinded phase included a flexible duration of up to a maximum of 24 months. The median treatment time was 20 months in the fingolimod arm and 18 months in the interferon beta-1a arm. After the end of the blinded phase of the study, the children and adolescents were able to switch to or continue treatment with fingolimod within an open extension phase (up to 5 years). The extension phase of the study is still ongoing. The present benefit assessment is based exclusively on data from the blinded phase of the study.

Relevant patient populations

Patient population a2) includes children and adolescents (≥ 10 and < 18 years of age) with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapy is indicated. These patients represent a sub-population of the PARADIGMS study. When operationalising the corresponding patient group, the criterion "change of basic therapy" must be taken into account; this was not done by the pharmaceutical company in the dossier.

As a result, in the sub-population operationalised by the pharmaceutical company, about 70% of the children and adolescents received interferon beta-1a therapy prior to the start of study and showed highly active RRMS. For these patients, the criterion "change within the basic therapeutic agents" is not fulfilled when they are included in the comparator arm of the study because they continued the (obviously inadequate) interferon beta-1a therapy within the study. This continuation of an inadequate therapy does not correspond to the implementation of the appropriate comparator therapy.

However, the pharmaceutical company also presented subgroup analyses for the sub-population that had operationalised in which subgroups are subdivided according to the type of previous therapy (interferon beta-1a vs interferon beta-1b vs glatiramer acetate). Therefore, for the present benefit assessment, the subgroup data of the children and

adolescents previously treated with interferon beta-1b and glatiramer acetate are used because a change within the basic therapy has taken place for this population. This sub-population relevant for the benefit assessment comprises nine patients under fingolimod therapy and 11 patients under interferon beta-1a therapy. On average, the children and adolescents were 15 to 16 years old. At the start of study, the median EDSS was 2.0 in the fingolimod arm and 1.5 in the interferon beta-1a arm. On average, the children and adolescents had 1.7 (fingolimod arm) and 1.5 relapses (interferon beta-1a arm) in the year before the start of study. Overall, the patient characteristics between the treatment groups are sufficiently balanced against the background of the small number of cases. The only major difference is in the gender ratio: In the fingolimod arm all children and adolescents were female; in the interferon beta-1a arm, only one third of the children and adolescents were female.

Extent and probability of the additional benefit

Mortality

No deaths occurred in the blinded phase of the PARADIGMS trial.

Morbidity

Confirmed relapses (EDSS based)

To assess the confirmed relapses, two operationalisations are used (annual rate of confirmed relapses and time to first confirmed relapse). Both operationalisations show an effect estimate in favour of fingolimod in comparison with interferon beta-1a. However, only the endpoint “time to the first confirmed relapse” shows a statistically significant advantage for treatment with fingolimod compared to treatment with interferon beta-1a. Data on the median time to the first confirmed relapse are not available for both treatment arms. However, in the endpoint “annual rate of confirmed relapses”, there is no statistically significant difference.
However, the endpoint “time to the first confirmed relapse” does not allow conclusions to be drawn about the number of annual relapses, which is of great importance for patients in assessing the disease relapses. Therefore, the extent of the advantage in the “time to the first confirmed relapse” cannot be quantified.
However, overall, an advantage of fingolimod over interferon beta-1a is derived for the endpoint “disease relapses” based on “time to the first confirmed relapse”.

Confirmed change in disability (EDSS based)

To assess the confirmed change in disability, the operationalisations “confirmed disability progression” and “confirmed disability improvement” are used. For both operationalisations, there is no statistically significant difference between the treatment groups. Therefore, neither an advantage nor a disadvantage for the therapy with fingolimod can be derived in comparison to a therapy with interferon beta-1a.

Quality of life

PedsQL

The health-related quality of life was measured using PedsQL. The PedsQL is a generic, validated questionnaire for self-determination of health-related quality of life in children and adolescents. For the benefit assessment, the continuous analyses of the overall PedsQL score are used. For the mean difference pooled over the sub-population after pretreatment, a statistically significant advantage of fingolimod in comparison to interferon beta-1a is shown. In order to assess the clinical relevance, Hedges’ g was estimated on the basis of effect estimates. The calculation shows an effect in the order of 1 standard deviation for the effect estimator (Hedges’ g: 0.97 [−0.02; 1.96).] However, because of the small number of cases, the estimates for the 95% confidence interval are uncertain and, in terms of statistical significance, inconsistent with the result for the mean difference. The confidence interval therefore cannot be used to estimate the relevance of the effect. Because of the magnitude of the effect described (approx. 1 standard deviation), an advantage for treatment with fingolimod over interferon beta-1a therapy in the endpoint health-related quality of life is nevertheless derived for this endpoint in the specific data basis. However, because of its unclear clinical relevance, it is non-quantifiable.

Side effects

The number of SAEs and therapy discontinuations because of AEs was low in both treatment arms. However, because of the very small number of patients, no reliable statements on the damage potential can be derived; thus no advantage or disadvantage for fingolimod compared to interferon beta-1a can be derived from the data available.

Overall assessment

The benefit assessment was based on the randomised, double-blind, and actively controlled PARADIGMS study comparing fingolimod with interferon beta-1a (intramuscularly applied) in paediatric and adolescent patients with relapsing-remitting multiple sclerosis. Patient population a2) includes children and adolescents (≥ 10 and < 18 years of age) with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapy is indicated. These patients represent a sub-population of the PARADIGMS study.

The morbidity endpoint “confirmed relapses” shows a statistically significant advantage for treatment with fingolimod compared to treatment with interferon beta-1a for the “time to the first confirmed relapse”. However, this statistically significant advantage is not reflected in the annual relapse rate. Statements about a reduction in the overall number of relapses can therefore not be made. Consequently, the advantage for fingolimod cannot be quantified on the basis of “time to the first confirmed relapse” alone.

In the change in disability between baseline and end of study, there are no statistically significant differences between treatment groups.

In the endpoint category of “health-related quality of life”, a statistically significant advantage of fingolimod over interferon beta-1a is observed. However, the assessment of the clinical

relevance of this statistically significant benefit is subject to uncertainty. The extent of the benefit can therefore not be quantified.

In the endpoint category of “side effects”, neither advantages nor disadvantages can be derived for fingolimod compared to interferon beta-1a. Against the background of the low number of patients on which this assessment was based, the damage potential of fingolimod cannot be conclusively assessed.

The statistically significant effects in favour of fingolimod in the morbidity endpoint “time to the first confirmed relapse” and the quality of life are classified as non-quantifiable with respect to extent. Furthermore, the damage potential of fingolimod cannot be conclusively assessed based on the low number of patients.

In the overall view, fingolimod thus has a non-quantifiable additional benefit compared to interferon beta-1a.

Reliability of data (probability of additional benefit)

The additional benefit is assessed on the basis of a randomised, double-blind, and direct comparison study. For the present benefit assessment, however, only the pretreated children and adolescents (≥ 10 and < 18 years) with highly active relapsing-remitting multiple sclerosis for whom a change within the basic therapy is indicated were relevant. As a result, out of a total of 215 children and adolescents included in the PARADIGMS study, only 20 patients (9 patients in the fingolimod arm and 11 patients in the interferon beta-1a arm) were included in the benefit assessment. The sub-population relevant for the benefit assessment thus comprises a very small number of patients, which is why the significance of the available data is subject to great uncertainty overall.

Against this background, the reliability of data is classified as a hint.

On patient group b1): (rapidly progressing severe RRMS, therapy-naïve)

The pharmaceutical company submits the PARADIGMS study for the assessment of the additional benefit of fingolimod over therapy with interferon beta-1a for the treatment of therapy-naïve children and adolescents with rapidly evolving severe relapsing-remitting multiple sclerosis.

Information on the study characteristics can be found under “On patient group a2)”.

Relevant patient populations

Patient population b1) includes children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received disease-modified therapy.

These patients represent a sub-population of the PARADIGMS study. Disability progression is a differentiation criterion between highly active relapsing-remitting multiple sclerosis and rapidly evolving severe relapsing-remitting multiple sclerosis relevant for this sub-population. Therefore, within the framework of the comments procedure, the pharmaceutical company submitted evaluations for patients with rapidly evolving severe relapsing-remitting multiple sclerosis in which at least two relapses and at least a Gd lesion occurred during the previous twelve months of study inclusion. In addition, the children and adolescents had to show a disability progression for inclusion in the study. This was operationalised using an EDSS value of ≥ 1. Even if this operationalisation does not allow conclusions to be drawn as to

whether the disability progression to study inclusion has occurred in the last twelve months (as a result of the relapses), the operationalisation presented for the definition of the sub-population to be assessed is regarded as a sufficient approximation. However, it must be taken into account that it cannot be ruled out that the evaluation also included patients who had no disability progression in the twelve months before the start of study and therefore did not fully correspond to the therapeutic indication.
The sub-population relevant for the benefit assessment comprises 17 patients under fingolimod therapy and 12 patients under interferon beta-1a therapy. On average, the children and adolescents were 15 years old. At the start of study, the median EDSS value was 2.0 in both arms. On average, the children and adolescents had 2.5 (fingolimod arm) and 2.2 relapses (interferon beta-1a arm) in the year before the start of study.

Extent and probability of the additional benefit

Mortality

No deaths occurred in the blinded phase of the PARADIGMS trial.

Morbidity

Confirmed relapses (EDSS based)

To assess the confirmed relapses, two operationalisations are used (annual rate of confirmed relapses and time to first confirmed relapse). Both operationalisations show an effect estimate in favour of fingolimod in comparison with interferon beta-1a. However, a statistically significant advantage of fingolimod compared to interferon beta-1a can only be seen in the “annual rate of confirmed relapses”.

Confirmed change in disability (EDSS based)

To assess the confirmed change in disability, the operationalisations “confirmed disability progression” and “confirmed disability improvement” are used. While there is no statistically significant difference between the treatment groups for the confirmed disability progression, a statistically significant advantage in favour of fingolimod over interferon beta-1a is shown for the improvement of disability.

Quality of life

PedsQL

The health-related quality of life was measured using PedsQL. The PedsQL is a generic, validated questionnaire for self-determination of health-related quality of life in children and adolescents. There is no statistically significant difference between the treatment groups. Therefore, neither an advantage nor a disadvantage for the therapy with fingolimod can be derived in comparison to a therapy with interferon beta-1a.

Side effects

For the endpoint SAE, there are no statistically significant differences between the two treatment groups. There was not termination of therapy because of AE. However, because of the very small number of patients, no reliable statements on the damage potential can be derived; thus no advantage or disadvantage for fingolimod compared to interferon beta-1a can be derived from the data available.

Overall assessment

The benefit assessment was based on the randomised, double-blind, and actively controlled PARADIGMS study comparing fingolimod with interferon beta-1a (intramuscularly applied) in paediatric and adolescent patients with relapsing-remitting multiple sclerosis. Patient population b1) includes therapy-naïve children and adolescents (≥ 10 and < 18 years of age) with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI. These patients represent a sub-population of the PARADIGMS study.

In the morbidity endpoint “confirmed relapses”, the annual relapse rate shows a statistically significant advantage for treatment with fingolimod over interferon beta-1a therapy. In contrast, there was no statistically significant difference between the treatment groups in the time to the first confirmed relapse. The morbidity endpoint “change of disability” between baseline and end of study shows a statistically significant difference in the improvement of disability in favour of fingolimod compared to interferon beta-1a. However, in terms of disability progression, there are no statistically significant differences between the two treatment groups. Considering that there is insufficient evidence that the progression of disability among the children and adolescents included has occurred within the previous twelve months and that these fully correspond to the target population, there are uncertainties to the extent that the benefits in the endpoints “annual relapse rate” and “improvement of disability” cannot be conclusively assessed. The extent of the additional benefit is therefore non-quantifiable for the relevant target population.

There is no statistically significant difference between fingolimod and interferon beta-1a in the endpoint categories of “health-related quality of life” and “side effects”.

The statistically significant effects in favour of fingolimod in the morbidity endpoints “annual relapse rate” and “improvement of disability” are non-quantifiable with respect to extent because of the existing uncertainties. Furthermore, it could not be proven that treatment with fingolimod has a positive effect on the quality of life of children and adolescents. Furthermore, the damage potential of fingolimod cannot be conclusively assessed based on the low number of patients. The overall benefits of fingolimod can therefore not be quantified on the basis of the submitted data.

In the overall view, fingolimod thus has a non-quantifiable additional benefit compared to interferon beta-1a.

Reliability of data (probability of additional benefit)

The additional benefit is assessed on the basis of a randomised, double-blind, and direct comparison study. For the present benefit assessment, however, only the therapy-naïve children and adolescents (≥ 10 and < 18 years) with rapidly evolving severe relapsing-remitting multiple sclerosis were relevant. As a result, out of a total of 215 children and adolescents included in the PARADIGMS study, only 29 patients (17 patients in the fingolimod arm and 12 patients in the interferon beta-1a arm) were included in the benefit assessment. The sub-population relevant for the benefit assessment thus comprises a very small number of patients, which is why the significance of the available data is subject to great uncertainty overall.

Against this background, the reliability of data is classified as a hint.

On patient group b2): (rapidly evolving severe RRMS, previously treated)

No data were submitted for the assessment of the additional benefit of fingolimod over therapy according to the doctor's instructions for the treatment of children and adolescents with rapidly evolving severe relapsing-remitting multiple sclerosis despite treatment with disease modifying therapy. The PARADIGMS study cannot be used to derive an additional benefit because all children and adolescents included in the comparator arm of the study received interferon beta-1a independently of the previous therapy. Consequently, the appropriate comparator therapy "therapy according to the doctor's instructions" has not been implemented. Although the active ingredient natalizumab is not approved for the present indication, it should have been used as an escalation therapy within the framework of a therapy according to the doctor's instructions as a comparator.

As a result, for this patient group, no conclusions can be drawn about the additional benefit of fingolimod compared to the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present evaluation is the benefit assessment of the active ingredient fingolimod in a new therapeutic indication: The therapeutic indication of fingolimod to be assessed comprises only children and adolescents aged 10 and over with RRMS and is as follows: "Monotherapy for highly active relapsing-remitting multiple sclerosis in children and adolescents aged ≥ 10 and < 18 years in patients with highly active disease despite treatment with a full and adequate course with at least one disease modifying therapy or in patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy.

In the assessment, the patients were subdivided into the following groups:

a1) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom escalation of therapy is indicated;

a2) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapeutics is indicated;

b1) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received disease modifying therapy;

b2) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy.

On patient group a1):

The G-BA determined a therapy in accordance with the doctor's instructions as an appropriate comparator therapy.

For pretreated children and adolescents with highly active relapsing-remitting multiple sclerosis for whom escalation therapy is indicated, the pharmaceutical company does not provide relevant data of fingolimod compared to the appropriate comparator therapy. An additional benefit is therefore not proven.

On patient group a2):

Interferon beta-1a, interferon beta-1b, or glatiramer acetate (taking into account the approval status) was determined as an appropriate comparator therapy by the G-BA.

There are statistically significant advantages in the morbidity category "time to the first confirmed relapse" and quality of life. However, both advantages are non-quantifiable with respect to extent. Because of the very small number of patients on which the assessment was based, the statements are subject to a high degree of uncertainty overall; the reliability of data is thus classified as a hint.

For previously treated children and adolescents with highly active relapsing-remitting multiple sclerosis for whom a change within the basic therapy is indicated, there is therefore a hint for a non-quantifiable additional benefit of fingolimod compared to interferon beta-1a.

On patient group b1):

Interferon beta-1a, interferon beta-1b, or glatiramer acetate (taking into account the approval status) was determined as an appropriate comparator therapy by the G-BA.

There are statistically significant advantages in the morbidity endpoints "annual rate of relapse" and "improvement of disability". Considering that there is insufficient evidence that the progression of disability among the children and adolescents included has occurred within the previous twelve months and that these fully correspond to the target population, there are uncertainties that the benefits for the relevant target population cannot be quantified. Because of the very small number of patients on which the assessment was based, the statements are subject to a high degree of uncertainty overall; the reliability of data is thus classified as a hint.

For children and adolescents with rapidly evolving severe relapsing-remitting multiple sclerosis who have not yet received disease modifying therapy, there is therefore a hint for a non-quantifiable additional benefit of fingolimod over interferon beta-1a.

On patient group b2):

The G-BA determined a therapy in accordance with the doctor's instructions as an appropriate comparator therapy.

For children and adolescents with rapidly evolving severe relapsing-remitting multiple sclerosis despite treatment with disease modifying therapy, the pharmaceutical company does not provide relevant data on fingolimod compared to the appropriate comparator therapy. An additional benefit is therefore not proven.

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

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

The information on the number of patients corresponds to the information provided by the pharmaceutical company in Module 3B of the dossier (for patient populations a1 and a2) or in addition to the written statement ((for patient populations b1 and b2).

As a starting point for all four patient groups, the pharmaceutical company identified 406 (Number of children aged 10 and over with at least one prescription for disease modifying MS therapies in 2017) to 1420 (Prevalence of MS on the basis of nationwide accounting data from contract physicians across all health insurance funds) paediatric patients with relapsing-remitting multiple sclerosis in the SHI system. Based on the lower and upper limits shown, the pharmaceutical company calculates an average value of a total of 913 patients in the SHI target population.

The pharmaceutical company then derives the patient numbers for the individual sub-populations, based in particular on the proportional values of the PARADIGMS study.

Based on the comments of the pharmaceutical company and the main source submitted, the information on the number of patients in the SHI target population is not comprehensible and can therefore not be evaluated. The pharmaceutical company uses an analysis of the company Insight Health from the year 2017 (which is based on the SHI regulations implemented) as the essential data basis. The source of Insight Health only contains only one table of results. However, there is a lack of information on the methodological approach (among other things, information on data generation, composition of the sample, and representativeness as well as description and definition of the retrieval criteria). Moreover, the source does not provide any information on extrapolation to all national ordinances.

For other sources used by the pharmaceutical company, the reported values cannot be found. Furthermore, the selectivity of the study population limits the use of proportional values from clinical studies for epidemiological purposes.

2.3 Requirements for a quality-assured application

The requirements of the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of Gilenya® (active ingredient: Fingolimod) at the following publicly accessible link (last access: 2 May 2019):

https://www.ema.europa.eu/documents/product-information/gilenya-epar-product-information_de.pdf

For fingolimod, there are several Dear Healthcare Professional Communications referring to serious adverse reactions (including cardiac side effects, haemophagocytic syndrome with death, occurrence of PML, opportunistic infections) and the corresponding monitoring measures.

The European Medicines Agency will regularly evaluate new information on this medicinal product and, if necessary, update the summary of product characteristics. Consequently, the status of the summary of product characteristics must be reviewed for up-to-datedness, in particular against the background of the continuously increasing knowledge about the risk profile of fingolimod; changes must be taken into account accordingly.

The initiation and monitoring of treatment must be carried out by a neurologist with experience in the treatment of multiple sclerosis.

In accordance with the guidelines of the European Medicines Agency (EMA) regarding additional risk minimisation measures, the pharmaceutical company must provide a check-list for doctors (including information on the fingolimod Intensive Monitoring Programme, on the outcome of pregnancies under fingolimod therapy, and on the fingolimod Pregnancy Registry) as well as a reminder card for all patients, their parents, and caregivers.

There are only very few data for use in children aged 10–12 years, children under 40 kg, or children of Tanner stage < 2. Long-term safety data for children and adolescents are not available.

2.4 Treatment costs

The treatment costs are based on the contents of the summary of product characteristics and the information listed in the LAUER-TAXE® (last revised: 01 June 2019).

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				
Fingolimod	continuous, 1 × daily	365	1	365
Appropriate comparator therapy				
Patient populations a1) und b2)				
Therapy according to the doctor's instructions	patient-individualized			
Patient populations a2) und b1)				
Interferon beta-1a	continuously, 1 × weekly	52	1	52
Interferon beta-1b	continuously, every 2 days	182.5	1	182.5
Glatiramer acetate	continuous, 1 × daily	365	1	365

Usage and consumption:

For the cost representation, only the dosages of the general case are considered. Patient-specific dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs. For fingolimod, the dosage for children and adolescents (from the age of 10 years) varies depending on body weight: Children and adolescents ≤ 40 kg BW receive 0.25 mg once daily; from 40 kg BW, 0.5 mg once daily.

The average body measurements from the official representative statistics "Microcensus 2017 - body measurements of the population" were used to calculate the dosages as a function of the body weight (the average body weight of 10-year-olds is 37.6 kg; the average body weight of 17-year-olds is 67 kg).[2]

For the active ingredient interferon beta-1a, no concrete dose recommendations are given for children and adolescents in the summary of product characteristics. The cost calculation is thus based on the dose recommendations for adults.

In accordance with the summary of product characteristics, the active ingredient interferon beta-1b should not be used in children under 12 years of age.

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/oowa921-install/servlet/oowa/aw92/dboowasys921.xwdevkit/xwd_init?gbe.isgbetol/xs_start_neu/&p_aid=i&p_aid=31629795&nummer=223&p_sprache=D&p_indsp=-&p_aid=29298335

The administration of glatiramer acetate is not recommended for children and adolescents between 10 and 12 years of age.

Designation of the therapy	Dosage/ application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ Patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Fingolimod	0.25 mg - 0.5 mg	0.25 mg - 0.5 mg	1 × 0.25 mg - 1 × 0.5 mg	365	365 × 0.25 mg - 365 × 0.5 mg
Appropriate comparator therapy					
Patient populations a1) und b2)					
Therapy according to the doctor's instructions	patient-individualized				
Patient populations a2) und b1)					
Interferon beta-1a	30 µg	30 µg	1 × 30 µg	52	52 × 30 µg
Interferon beta-1b	250 µg	250 µg	1 × 250 µg	182.5	182.5 × 250 µg
Glatiramer acetate	20 mg	20 mg	1 × 20 mg	265	365 × 20 mg

Costs:

Costs of the medicinal product:

To facilitate comparability, the pharmaceutical costs were approximated both on the basis of the pharmacy sales price level and also the price less 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 pharmaceutical costs were then calculated on the basis of the costs per pack less the statutory rebates.

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Fingolimod 0.25 mg	28 HC	€ 931.41	€ 1.77	€ 50.96	€ 878.68
Fingolimod 0.5 mg	98 HC	€ 6,303.61	€ 1.77	€ 356.73	€ 5,945.11
Appropriate comparator therapy					
Interferon beta-1a	4 PEN	€ 1,781.88	€ 1.77	€ 246.77	€ 1,533.34
Interferon beta-1b	42 PSI	€ 3,936.51	€ 1.77	€ 245.85	€ 3,688.89
Glatiramer acetate	90 PFS	€ 3,400.69	€ 1.77	€ 163.66	€ 3,235.26
Therapy according to the doctor's instructions	patient-individualized				
Abbreviations: PFS = pre-filled syringes; HC = hard capsules; PEN = injection solution in a pre-fabricated pen; PSI = powder and solvent for solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 01 June 2019

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 drug to be evaluated and the appropriate comparator therapy according to the summary of product characteristics, the costs incurred for this must be taken into account as costs for additional SHI services required.

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.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additional SHI services required had to be taken into account.

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its meeting on 13 January 2015.

The appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redetermined the appropriate comparator therapy at its meeting on 08 January 2019 .

On 19 December 2018, the pharmaceutical company submitted a dossier for the benefit assessment of fingolimod to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 19 December 2018 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 fingolimod .

The dossier assessment by the IQWiG was submitted to the G-BA on 28 March 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 01 April 2019. The deadline for submitting written statements was 23 April 2019.

The oral hearing was held on 06 May 2019.

By letter dated 06 May 2019, 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 29 May 2019.

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 meetings.

The evaluation of the written statements received and the oral hearing was discussed at the meeting of the subcommittee on 12 June 2019, and the proposed resolution was approved.

At its meeting on 20 June 2019 , the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	13 January 2015	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	08 January 2019	Redefinition of the appropriate comparator therapy
Working group Section 35a	29 April 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2019	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 May 2019 22 May 2019 5 June 2019	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	12 June 2019	Concluding discussion of the proposed resolution
Plenum	20 June 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 June 2019

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

Prof. Hecken