Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Dimethyl fumarate (new therapeutic indication: relapsing remitting multiple sclerosis, ≥ 13 years)

of 18 January 2024

Contents

1. Legal basis ... 2

2. Key points of the resolution ... 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy ... 4

2.1.1 Approved therapeutic indication of Dimethyl fumarate (Tecfidera) in accordance with the product information ... 4

2.1.2 Appropriate comparator therapy ... 4

2.1.3 Extent and probability of the additional benefit ... 8

2.1.4 Limitation of the period of validity of the resolution ... 8

2.1.5 Summary of the assessment ... 9

2.2 Number of patients or demarcation of patient groups eligible for treatment ... 10

2.3 Requirements for a quality-assured application ... 10

2.4 Treatment costs ... 10

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product ... 13

3. Bureaucratic costs calculation ... 16

4. Process sequence ... 16

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 active ingredient dimethyl fumarate was listed for the first time on 1 March 2014 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. On 13 May 2022, dimethyl fumarate received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 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, 12.12.2008, p. 7).

The pharmaceutical company has 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 dimethyl fumarate with the new therapeutic indication "for the treatment of adult and paediatric patients aged 13 years and older with relapsing

remitting multiple sclerosis (RRMS)" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

By resolution of 16 June 2022, the G-BA provisionally suspended the resolution on the benefit assessment according to Section 35a SGB V for the medicinal product Tecfidera with the active ingredient dimethyl fumarate in the new therapeutic indication for the treatment of children and adolescents aged 13 years and older with relapsing-remitting multiple sclerosis, as there was a dispute between the pharmaceutical company and the European Commission regarding the scope of the dossier protection of the medicinal product Tecfidera with the active ingredient dimethyl fumarate in this therapeutic indication.

Pursuant to the European Commission's implementing decision C(2023)3067 (final)[1] of 2 May 2023 amending the marketing authorisation granted by resolution C(2014)601 (final) for the medicinal product Tecfidera containing the active ingredient dimethyl fumarate, it was determined that - in the light of the final judgement of the European Court of Justice of 16 March 2023 - the marketing protection pursuant to Article 14 paragraph 11 of Regulation (EC) No. 726/2004 for the medicinal product Tecfidera may be extended for a further year, thus ending the marketing protection for the medicinal product Tecfidera on 2 February 2025.

As a result, the requirements for adopting a resolution in accordance with Section 35a, paragraph 1 SGB V were therefore met for the active ingredient dimethyl fumarate in this therapeutic indication, so that the G-BA resumed the benefit assessment procedure with its resolution of 6 July 2023 as at the time of the suspension of the procedure.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 16 October 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of dimethyl fumarate 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 [2] was not used in the benefit assessment of dimethyl fumarate.

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:

1 https://ec.europa.eu/health/documents/community-register/2023/20230502159131/dec_159131_en.pdf

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

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

2.1.1 Approved therapeutic indication of Dimethyl fumarate (Tecfidera) in accordance with the product information

Tecfidera is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

Therapeutic indication of the resolution (resolution of 18 January 2024):

Tecfidera is indicated for the treatment of paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents aged ≥ 13 to < 18 years with relapsing remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pre-treated with disease-modifying therapy whose disease is not highly active

Appropriate comparator therapy for dimethyl fumarate:

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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

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

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

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

on 1. The following active ingredients are generally approved for the treatment of relapsing remitting multiple sclerosis (RRMS) in children and adolescents: fingolimod, glatiramer acetate, interferon-beta 1a, interferon-beta 1b and teriflunomide.

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, 20 January 2022 (new therapeutic indication)
- 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 (patient group b), 19 May 2022 (patient group a)

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 indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

For the active ingredient dimethyl fumarate, a marketing authorisation was extended for children and adolescents from ≥ 13 to < 18 years with relapsing remitting multiple sclerosis (RRMS). 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).

Considering the active ingredient nature of dimethyl fumarate, it is assumed that children and adolescents with highly active RRMS disease do not represent the target population of dimethyl fumarate despite receiving disease-modifying therapy. Consequently, this patient group is not the subject of the present benefit assessment.

For children and adolescents aged ≥ 13 to < 18 years with relapsing remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pre-treated with disease-modifying therapy whose disease is not highly active, the following active ingredients are available according to the marketing authorisation: glatiramer acetate, interferon-beta 1a, interferon-beta 1b and teriflunomide. Since December 2022, the medicinal product Avonex™ with the active ingredient interferon-beta 1a has explicitly no longer been approved for the treatment of children and adolescents with relapsing multiple sclerosis.

Against the background of the restricted marketing authorisation for the active ingredient interferon-beta 1a and the current body of evidence, which does not allow a reliable assessment of the efficacy and safety of Avonex™ or interferon-beta 1a for the treatment of children and adolescents with relapsing multiple sclerosis, the active ingredient interferon-beta 1a is not considered to be an equally appropriate therapy option.

The active ingredient teriflunomide has been approved since June 2021 for the treatment of children and adolescents aged 10 years and older with relapsing-remitting multiple sclerosis. Guidelines recommend teriflunomide as an active ingredient of efficacy category 1 as a therapy option for children and adolescents with a mild or moderate form of multiple sclerosis.

In the overall assessment of the body of evidence, the active ingredients interferon-beta 1b, glatiramer acetate and teriflunomide are to be regarded as equally appropriate options with regard to their therapeutic use in this therapeutic indication.

In summary, for children and adolescents aged ≥ 13 to < 18 years with relapsing-remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active, the active ingredients interferon-beta 1b, glatiramer acetate or teriflunomide are determined as the appropriate comparator therapy. 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.

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

Change of the appropriate comparator therapy

For children and adolescents aged ≥ 13 to < 18 years with relapsing-remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active, the active ingredients interferon-beta 1a, interferon-beta 1b or glatiramer acetate were previously considered as the appropriate comparator therapy.

The active ingredient teriflunomide, which has been approved since 2021, provides a further option for the treatment of children and adolescents with relapsing-remitting multiple sclerosis.

In December 2022, the marketing authorisation for the medicinal product Avonex™ with the active ingredient interferon-beta 1a was restricted to the treatment of adults with relapsing multiple sclerosis. The decision of the European Medicines Agency (EMA)[3] took into account the aggregated evidence, which does not provide robust evidence for the efficacy of interferon-beta 1a in the treatment of children and adolescents with relapsing-remitting multiple sclerosis. Furthermore, the EMA summarises that the available evidence based on the CONNECT and PARADIGMS studies, in which the active ingredients dimethyl fumarate and fingolimod were compared with interferon-beta 1a, does not ensure that the safety of Avonex™ in the treatment of children and adolescents is the same as in adults. Based on this

3 https://www.ema.europa.eu/en/documents/variation-report/avonex-h-c-102-ii-0193-epar-assessment-report-variation_en.pdf-0

new situation, it is not tenable to continue considering the active ingredient interferon-beta 1a as an appropriate therapy option for the treatment of children and adolescents with relapsing-remitting multiple sclerosis.

Against the background of the current body of evidence, the extension of the marketing authorisation and the increasing significance of the active ingredient teriflunomide in healthcare as well as the restriction on authorisation for the medicinal product Avonex™ with the active ingredient interferon-beta 1a, the G-BA considers it justified to amend the appropriate comparator therapy at this point in time and to adapt it to the current state of medical knowledge. Accordingly, the active ingredients interferon-beta 1b, glatiramer acetate or teriflunomide are designated as the appropriate comparator therapy.

2.1.3 Extent and probability of the additional benefit

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

For children and adolescents aged ≥ 13 to < 18 years with relapsing-remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active, the additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submitted data from the randomised open-label CONNECT study Part 1, in which dimethyl fumarate was compared with the active ingredient interferon-beta 1a (medicinal product: Avonex™) over a period of 96 weeks.

For children and adolescents aged ≥ 13 to < 18 years with relapsing-remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active, the active ingredients interferon-beta 1b, glatiramer acetate or teriflunomide were determined as the appropriate comparator therapy.

The appropriate comparator therapy was therefore not implemented in the CONNECT study Part 1, in which the patients in the comparator arm received the medicinal product Avonex™ with the active ingredient interferon-beta 1a.

For children and adolescents aged ≥ 13 to < 18 years with relapsing-remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active, no data are available for the comparison of dimethyl fumarate with the appropriate comparator therapy. Accordingly, there are no relevant data for the benefit assessment of dimethyl fumarate.

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

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of dimethyl fumarate finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product.

In the present case, the limitation is justified by the below-mentioned objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

Due to the present change in the appropriate comparator therapy, the G-BA considers it appropriate to limit the resolution on the additional benefit of dimethyl fumarate. The limitation enables the pharmaceutical company to submit suitable evaluations, which correspond to the appropriate comparator therapy determined by the present resolution, in a new dossier in a timely manner. For this purpose, the G-BA considers a limitation of the period of validity of the resolution until 1 July 2024 to be appropriate.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product Tecfidera with the active ingredient dimethyl fumarate recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of dimethyl fumarate (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit is considered as being not proven. The possibility that a benefit assessment for the medicinal product Tecfidera with the active ingredient dimethyl fumarate can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient dimethyl fumarate.

The therapeutic indication assessed here is as follows: Tecfidera is indicated for the treatment of paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

For children and adolescents aged ≥ 13 to < 18 years with relapsing-remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active, the G-BA determined the active ingredients interferon-beta 1b, glatiramer acetate or teriflunomide as the appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company presented the CONNECT study Part 1, in which dimethyl fumarate was compared with the active ingredient interferon-beta 1a (medicinal product: Avonex™). The appropriate comparator therapy was not implemented in the study submitted for the benefit assessment.

In the overall assessment, there are therefore no suitable data for the comparison of dimethyl fumarate with the appropriate comparator therapy. Thus, for children and adolescents aged ≥ 13 to < 18 years with relapsing-remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pretreated with disease-modifying therapy whose disease is not highly active, an additional benefit of dimethyl fumarate is not proven.

The period of validity of the resolution is limited to 1 July 2024.

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 present resolution is based on the information on the number of patients from the benefit assessment resolution on teriflunomide (of 20 January 2022).

These were determined for children and adolescents aged ≥ 10 years to < 18 years with otherwise identical characteristics to those of the present patient population. The information is subject to uncertainties overall. In particular, it can be assumed that the lower age range (≥ 13 years to < 18 years instead of ≥ 10 years to < 18 years) is an overestimation of the patient numbers.

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 Tecfidera (active ingredient: dimethyl fumarate) at the following publicly accessible link (last access: 15 December 2023):

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

Treatment with dimethyl fumarate should only be initiated and monitored by specialists in neurology or neurology and psychiatry or paediatrics with specialisation in neuropaediatrics who are experienced in the treatment of patients with multiple sclerosis.

A Direct Healthcare Professional Communication ("Rote-Hand-Brief") is available for dimethyl fumarate for risk minimisation of progressive multifocal leukoencephalopathy (PML).

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2024).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

To determine consumption, the average body measurements of the official representative statistics "Microcensus 2017 – body measurements of the population" are applied for dosages depending on body weight (average body weight at age ≥ 13 years < 14 years: 52.4 kg).[4] A dosage recommendation for the active ingredient teriflunomide is available for children and adolescents depending on body weight (children and adolescents with a body weight > 40 kg: 14 mg once daily).

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				
Dimethyl fumarate	Continuously, 2 x daily	365	1	365
Appropriate comparator therapy				
Glatiramer acetate	Continuously, 1 x daily	365	1	365
Interferon beta 1b	Continuously, every 2 days	182.5	1	182.5
Teriflunomide	Continuously, 1 x daily	365	1	365

4 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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					
Dimethyl fumarate	240 mg	480 mg	2 x 240 mg	365	730 x 240 mg
Appropriate comparator therapy					
Glatiramer acetate	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Interferon beta 1b	250 µg	250 µg	1 x 250 µg	182.5	182.5 x 250 µg
Teriflunomide	14 mg	14 mg	1 x 14 mg	365	365 x 14 mg

Costs:

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

Costs of the medicinal products:

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					
Dimethyl fumarate	168 ECC	€ 2,748.58	€ 2.00	€ 153.68	€ 2,592.90
Appropriate comparator therapy					
Glatiramer acetate	90 PS	€ 3,401.02	€ 2.00	€ 163.66	€ 3,235.36
Interferon beta 1b	42 PSI	€ 4,472.02	€ 2.00	€ 216.09	€ 4,253.93
Teriflunomide	28 FCT	€ 610.60	€ 2.00	€ 75.84	€ 532.76

Abbreviations:
ECC = enteric-coated hard capsule; PS = pre-filled syringes; FCT = film-coated tablets; PSI = powder and solvent for solution for injection

LAUER-TAXE® last revised: 01 January 2024

Costs for additionally required SHI services:

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

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

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 additionally required SHI services need to be taken into account.

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

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

Basic principles of the assessed medicinal product

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

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

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the

pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

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

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

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

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

Concomitant active ingredient:

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

Children and adolescents aged ≥ 13 to < 18 years with relapsing remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy or children and adolescents pre-treated with disease-modifying therapy whose disease is not highly active

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

References:
Product information for dimethyl fumarate (Tecfidera); last revised: May 2022

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 7 September 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 15 February 2022.

On 10 June 2022, the pharmaceutical company submitted a dossier for the benefit assessment of dimethyl fumarate to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 6 July 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient dimethyl fumarate.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 October 2023, and the written statement procedure was initiated with publication on the G-BA website on 16 October 2023. The deadline for submitting statements was 6 November 2023.

The oral hearing was held on 27 November 2023.

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 9 January 2024, and the proposed resolution was approved.

At its session on 18 January 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 September 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	15 February 2022	New implementation of the appropriate comparator therapy
Working group Section 35a	14 November 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	27 November 2023	Conduct of the oral hearing
Working group Section 35a	5 December 2023 19 December 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	9 January 2024	Concluding discussion of the draft resolution
Plenum	18 January 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 18 January 2024

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

Prof. Hecken