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 Teriflunomide (new therapeutic indication: relapsing remitting multiple sclerosis, 10 - 17 years)

of 20 January 2022

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient teriflunomide was listed for the first time on 1 October 2013 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 18 June 2021, teriflunomide 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 European 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).

On 16 July 2021, i.e. at the latest within four weeks after the disclosure of the pharmaceutical company on the approval of a new area of application, the pharmaceutical company has submitted a dossier in due time 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 teriflunomide with the new therapeutic indication "Aubagio is indicated for the treatment of adult patients and of children and adolescents aged 10 years and older with relapsing remitting multiple sclerosis (MS).".

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 1 November 2021, 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 teriflunomide compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of teriflunomide.

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

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

2.1.1 Approved therapeutic indication of Teriflunomide (Aubagio) in accordance with the product information

AUBAGIO is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS). See section 5.1 for more information on the patients in whom efficacy has been demonstrated.

Therapeutic indication of the resolution (resolution of 20 January 2022):

Children and adolescents aged ≥ 10 to < 18 years with relapsing remitting multiple sclerosis.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents aged ≥ 10 to < 18 years with relapsing remitting multiple sclerosis who have not yet received disease-modifying therapy or children and adolescents pre-treated with disease-modifying therapy whose disease is not highly active

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

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. 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 Federal Joint Committee has already determined the patient-relevant advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

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

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
- Dimethyl fumarate: resolution according to Section 35a SGB V of 16 October 2014
- Fingolimod: resolution according to Section 35a SGB V of 1 October 2015 (reassessment after the deadline), 19 May 2016 (new therapeutic indication), 20 June 2019 (new therapeutic indication)
- Cladribine: resolution according to Section 35a SGB V of 17 May 2018
- Ocrelizumab: resolution according to Section 35a SGB V of 2 August 2018
- Extract from Cannabis sativa: resolution according to Section 35a SGB V of 1 November 2018 (reassessment after the deadline)
- Siponimod: resolution according to Section 35a SGB V of 20 August 2020
- Ozanimod: resolution according to Section 35a SGB V of 7 January 2021
- Ponesimod: resolution according to Section 35a SGB V of 2 December 2021

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

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

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

For the active ingredient teriflunomide, a marketing authorisation was extended for children and adolescents from ≥ 10 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).

Change of the appropriate comparator therapy

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

For children and adolescents aged ≥ 10 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 and interferon beta-1b.

For the treatment of relapsing remitting multiple sclerosis in children and adolescents, interferon beta-1a, interferon beta-1b and glatiramer acetate are considered to be basic therapeutics, taking into account the authorisation status. In the S2k guideline on the diagnosis and therapy of multiple sclerosis, the German Society for Neurology recommends starting therapy with one of the beta interferon preparations or a glatirameroid in children and adolescents with a diagnosis of RRMS and mild or moderate forms of disease progression. In the overall assessment of the body of evidence, beta-interferons and glatiramer acetate are to be regarded as equivalent in terms of their therapeutic use.

For the active ingredient interferon beta-1a, proprietary medicinal products are available with different routes of administration (Rebif® SC; Avonex® IM) and different frequencies of administration. When determining the appropriate comparator therapy, the G-BA usually determines active ingredients independently of available proprietary medicinal products, provided that no limitations arise due to the therapeutic indication to be assessed (for example, with regard to certain dosage forms). In the treatment of relapsing remitting multiple sclerosis, there are no indication-specific criteria to be considered with regard to a route of administration. The available direct evidence on the comparison of the proprietary medicinal products Rebif® (INF-β 1a, SC) and Avonex® (INF-β 1a, IM) is assessed to the effect that the differences shown in the available studies are not to be assessed to the extent that one medicinal product is to

be preferred to the other as a rule. For the patient-relevant endpoint "prevention of disability progression", no difference in favour of one of the preparations could be proven in adults so far.

Accordingly, for children and adolescents aged ≥ 10 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 and glatiramer acetate are determined to be equally appropriate therapy options, taking into account the authorisation status. The marketing authorisation and product information of the respective medicinal products must be taken into account here.

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

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

2.1.3 Extent and probability of the additional benefit

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

Children and adolescents aged ≥ 10 to < 18 years with relapsing remitting multiple sclerosis who have not yet received disease-modifying therapy or children and adolescents pre-treated with disease-modifying therapy whose disease is not highly active

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of teriflunomide for the treatment of children and adolescents aged 10 years and older with relapsing remitting multiple sclerosis, the pharmaceutical company does not submit any data compared to the appropriate comparator therapy. An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient teriflunomide. The therapeutic indication assessed here is as follows: "AUBAGIO is indicated for the treatment of children and adolescents aged 10 years and older with relapsing remitting multiple sclerosis."

The assessment relates to children and adolescents aged ≥ 10 to < 18 years with relapsing remitting multiple sclerosis 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 G-BA determined interferon beta-1a or interferon beta-1b or glatiramer acetate as the appropriate comparator therapy, taking into account the authorisation status.

For the assessment of the additional benefit of teriflunomide for the treatment of children and adolescents aged 10 years and older with relapsing remitting multiple sclerosis, the

pharmaceutical company does not submit any data 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

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

The G-BA bases its resolution on the estimate of patient numbers derived by the pharmaceutical company in the dossier. Overall, the derivation of patient numbers is mathematically comprehensible, but subject to uncertainty. The upper limit given is to be regarded as overestimated, as the calculations are also based on data from patients aged 0 to 9 years and 18 to 19 years. The calculation for the lower limit of the target population is essentially based on an analysis of SHI prescriptions already carried out in the 2019[2] procedure for fingolimod, which was classified as not assessable.

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 Aubagio (active ingredient: teriflunomide) at the following publicly accessible link (last access: 30 September 2021):

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

Treatment with teriflunomide should be initiated and monitored by a specialist in neurology or by a specialist in neurology and psychiatry or by a specialist in paediatrics and adolescent medicine with specialisation in neuropaediatrics and experience in the treatment of multiple sclerosis.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide a discussion guide for doctors and health professionals as well as a patient information card. Both materials points, among others, to the teratogenic potential of teriflunomide.

2.4 Treatment costs

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

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

2 Resolution of 20 June 2019 on fingolimod (children and adolescents aged 10 years and older with highly active relapsing remitting multiple sclerosis)

of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. If the treatment duration is not limited, initial induction schemes are not considered for the cost representation. Patient-individual dose adjustments (e.g., because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For teriflunomide, the recommended dosage for children and adolescents (from the age of 10 years) varies depending on body weight: children and adolescents ≤ 40 kg body weight receive 7 mg teriflunomide 1 x daily, children and adolescents > 40 kg body weight receive 14 mg teriflunomide 1 x daily.

For dosages depending on body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied (average body weight: the average body weight of a 10-year-old child is 37.6 kg and that of a 17-year-old adolescent 67 kg.[3]

For the active ingredient interferon beta-1a, no specific dosage recommendations are given for children and adolescents in the product information, so that the dosage recommendations for adults are used for the cost calculation.

The active ingredients interferon beta-1b and glatiramer acetate are not to be used in children under 12 years of age according to the product information, as there are not enough data for this patient group in each case.

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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				
Teriflunomide	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Interferon beta-1a	continuously, 1 x every 7 days	52.1	1	52.1
Interferon beta-1b	continuously, every 2 days	182.5	1	182.5
Glatiramer acetate	continuously, 1 x daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average concumprion by potency
Medicinal product to be assessed					
Teriflunomide	7 mg - 14 mg	7 mg - 14 mg	1 x 7 mg - 1 x 14 mg	365	365 x 7 mg - 365 x 14 mg
Appropriate comparator therapy					
Interferon beta-1a	30 µg	30 µg	1 x 30 µg	52.1	52.1 x 30 µg
Interferon beta-1b	250 µg	250 µg	1 x 250 µg	182.5	182.5 x 250 µg
Glatiramer acetate	20 mg	20 mg	1 x 20 mg	365	365 x 20 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 usage. 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.

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					
Teriflunomide 7 mg	28 FCT	€ 1,030.11	€ 1.77	€ 0.00	€ 1,028.34
Teriflunomide 14 mg	84 FCT	€ 3,020.76	€ 1.77	€ 0.00	€ 3,018.99
Appropriate comparator therapy					
Interferon beta-1a 30 µg	4 PEN	€ 1,712.21	€ 1.77	€ 149.83	€ 1,560.61
Interferon beta-1b 250 µg	42 PSI	€ 4,156.82	€ 1.77	€ 271.43	€ 3,883.62
Glatiramer acetate 20 mg	90 PS	€ 3,400.98	€ 1.77	€ 163.66	€ 3,235.55
Abbreviations: PS = prefilled syringe; FCT = film-coated tablets; PEN = solution for injection in a pre-filled pen; PSS = powder and solvent for solution for injection					

LAUER-TAXE® last revised: 01 January 2022

Costs for additionally required SHI services:

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

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

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 had to be taken into account.

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 26 May 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 16 July 2021, the pharmaceutical company submitted a dossier for the benefit assessment of teriflunomide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 20 July 2021 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 teriflunomide.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 October 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 November 2021. The deadline for submitting written statements was 22 November 2021.

The oral hearing was held on 6 December 2021.

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 11 January 2022, and the proposed resolution was approved.

At its session on 20 January 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	26 May 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	30 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 December 2021	Conduct of the oral hearing
Working group Section 35a	14 December 2021 4 January 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	11 January 2022	Concluding discussion of the draft resolution
Plenum	20 January 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 January 2022

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

Prof. Hecken