Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Ponesimod (relapsing multiple sclerosis)

of 2 December 2021

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

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

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

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient ponesimod in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 June 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 14 June 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 September 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 ponesimod compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements

submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of ponesimod.

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

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

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

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

Therapeutic indication of the resolution (resolution from 02.12.2021):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined for patient population b) as follows:

b) Adult patients with relapsing forms of multiple sclerosis (RMS) with highly active disease despite disease-modifying therapy[2].

- alemtuzumab or fingolimod or natalizumab

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

2 An appropriate (pre)treatment usually lasts at least 6 months. Depending on relapse frequency and severity as well as disability progression, the treatment duration with disease-modifying therapy may be less than 6 months and must be justified.

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 benefit shall be preferred.

4: According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

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

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

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

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

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

- fampridine: resolution according to Section 35a SGB V of 2 August 2012
- teriflunomide: resolution according to Section 35a SGB V of 20 March 2014
- 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

Furthermore, the following therapy 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.

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

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

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

Azathioprine and mitoxantrone are only indicated for a limited sub-population of the patient population covered by the therapeutic indication due to their marketing authorisation. Azathioprine is indicated in relapsing multiple sclerosis when immunomodulatory therapy and therapy with beta interferons are not possible or a stable course has been achieved with previous therapy with azathioprine. Mitoxantrone is indicated for the treatment of patients with highly active, relapsing multiple sclerosis, associated with rapidly evolving disability, for which no alternative treatment options exist. Azathioprine and mitoxantrone are not considered as

appropriate comparator therapy due to their therapeutic indication, evidence and therapeutic value as reserve preparations in the treatment of RMS.

For patient group b), the following active ingredients are available in accordance with the marketing authorisation and taking into account the previously explained: alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, natalizumab, ocrelizumab, ofatumumab, ozanimod, peginterferon beta-1a, siponimod and teriflunomide.

Alemtuzumab, fingolimod and natalizumab, among others, are approved for disease-modifying monotherapy in adult patients with highly active, relapsing-remitting multiple sclerosis despite a full and adequate cycle of at least one disease-modifying therapy. Guidelines recommend the use of these highly active ingredients in adult patients who show highly active disease despite pretreatment with interferons or glatiramer acetate. For these patients, alemtuzumab, fingolimod and natalizumab are equally appropriate treatment options and, therefore, are determined to be the appropriate comparator therapy for adult patients with highly active disease despite disease-modifying therapy.

The therapy information on natalizumab and alemtuzumab must be taken into account. According to the product information of alemtuzumab, in particular, it should be noted that only its restrictive use is possible and it is not generally considered for all patients.

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 marketing authorisation and product information of the respective medicinal products must be taken into account.

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

2.1.3 Extent and probability of the additional benefit

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

b) <u>Adult patients with relapsing forms of multiple sclerosis (RMS) with highly active disease despite disease-modifying therapy.</u>

An additional benefit is not proven.

Justification:

The pharmaceutical company does not present any data for the assessment of the additional benefit of ponesimod for pretreated adults with highly active disease, compared to the appropriate comparator therapy. An additional benefit is not proven.

2.1.4 Summary of the assessment

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

Ponesimod is approved for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adult patients with relapsing forms of multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy.
b) Adult patients with relapsing forms of multiple sclerosis (RMS) with highly active disease despite disease-modifying therapy.

On patient population b)

The G-BA determined the active ingredients alemtuzumab, fingolimod or natalizumab as the appropriate comparator therapy.

For this patient group, the pharmaceutical company does not submit any data for the assessment of the additional benefit of ponesimod compared to the appropriate comparator therapy. An additional benefit is 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 comprehensible, but subject to uncertainty. This uncertainty results, in particular, from the fact that there is currently no uniform definition of high disease activity. The use of different selection criteria can therefore result in different percentages.

The current figures are higher, compared to the information in the resolution on ocrelizumab in the same therapeutic indication (relapsing multiple sclerosis) from 2018[3] However, the assumption of higher percentages of RMS seems plausible and is consistent with the current publication Flachenecker et al. (2020) based on percentage data reported by the DMSG MS registry from 2014 to 2018.

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

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Ponvory (active ingredient: ponesimod) at the following publicly accessible link (last access: 10 August 2021):

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

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2021).

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

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

The use of alemtuzumab is limited to two to four cycles.

According to the product information, continuation of therapy with natalizumab beyond this period of 2 years should only be considered if a new benefit-risk assessment has been carried out beforehand.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ponesimod	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Patient population b)				
Alemtuzumab	1st year: 5 consecutive days	1	5	5
	2nd year (3rd and 4th year if applicable): 3 consecutive days	1	3	3
Fingolimod	continuously, 1 x daily	365	1	365
Natalizumab	1 x every 28 days	13	1	13

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ponesimod	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Appropriate comparator therapy					
Patient population b)					
Alemtuzumab	12 mg	12 mg	1 x 12 mg	1st year: 5	1st year: 5 x 12 mg
				2nd year (3rd and 4th year if applicable) : 3	2nd year (3rd and 4th year if applicable): 3 x 12 mg
Fingolimod	0.5 mg	0.5 mg	1 x 0.5 mg	365	365 x 0.5 mg
Natalizumab	300 mg	300 mg	1 x 300 mg	13	13 x 300 mg

Costs:

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					
Ponesimod 20 mg	28 FCT	€ 1,869.28	€ 1.77	€ 103.48	€ 1,764.03
Appropriate comparator therapy					
Alemtuzumab 12 mg	1 CIS	€ 11,226.00	€ 1.77	€ 646.27	€ 10,577.96
Fingolimod 0.5 mg	98 HC	€ 5,936.23	€ 1.77	€ 0.00	€ 5,934.46
Natalizumab 300 mg	1 CIS	€ 2,428.12	€ 1.77	€ 135.39	€ 2,290.96
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 November 2021

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 standard expenditure in the course of the treatment are not shown.

For alemtuzumab, costs are regularly incurred for examining for both active and inactive ("latent") tuberculosis infections. The costs presented are a blood test (quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens specific for Mycobacterium tuberculosis-complex (except BCG)). The tuberculin skin test is not presented due to lack of sensitivity and specificity as well as the possibility of "sensitisation".

Designation of the therapy	Designation of the service	Number	Unit cost	Costsper patient per year
Appropriate comparator therapy for patient population b)				
Alemtuzumab	Quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens (at least ESAT-6 and CFP-10) specific for Mycobacterium tuberculosis-complex (except BCG) (GOP 32670)	1	€ 58.00	€ 58.00

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy sales price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active

ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

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

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

By letter dated 14 June 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 ponesimod.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 September 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 September 2021. The deadline for submitting written statements was 6 October 2021.

The oral hearing was held on 25 October 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 were discussed at the session of the subcommittee on 23 November 2021, and the proposed resolution was approved.

At its session on 2 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 January 2021	Determination of the appropriate comparator therapy
Working group Section 35a	19 October 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	25 October 2021	Conduct of the oral hearing
Working group Section 35a	2 November 2021 16 November 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	23 November 2021	Concluding discussion of the draft resolution
Plenum	2 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 December 2021

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

Prof. Hecken