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Ponesimod (multiple sclerosis) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ponesimod (multiple Sklerose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 September 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN	interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RMS	relapsing multiple sclerosis
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ponesimod. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 June 2021.

Research question

The aim of this report is to assess the added benefit of ponesimod in comparison with the ACT in adult patients with active relapsing multiple sclerosis (RMS).

The G-BA's specification of the ACT results in the research questions presented in Table 2.

Table 2: Research questions of the benefit assessment of ponesimod

Research question	Therapeutic indication	ACT[a]
1	Adult patients with active RMS without prior disease-modifying therapy or adult patients with prior disease-modifying therapy whose disease is not highly active	IFN-β 1a or IFN-β 1b or glatiramer acetate or ocrelizumab, taking into account approval status
2	Adult RMS patients with highly active disease despite treatment with disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, appropriate (prior) treatment typically must be administered for at least 6 months. Depending on the frequency and severity of relapses as well as disability progression, the duration of disease-modifying therapy can be less than 6 months and must be justified.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; RMS: relapsing multiple sclerosis

In this benefit assessment, the following terminology is used for the research questions:

- Research question 1: treatment-naive patients as well as pre-treated patients and patients without highly active RMS
- Research question 2: pre-treated patients with highly active RMS

For research question 1, the company departed from the G-BA's specification by identifying teriflunomide as an additional ACT option, alongside the options specified by the G-BA. However, the arguments presented by the company do not justify expanding the ACT by teriflunomide. Hence, the present benefit assessment was conducted using the ACT specified by the G-BA, disregarding the option of teriflunomide.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 12 months were used to derive added benefit.

Research question 1: treatment-naive patients as well as pre-treated patients and patients without highly active RMS

Study pool of the company

For research question 1, no relevant RCT was found for the comparison of ponesimod with the ACT specified by the G-BA. For this research question, the company submitted the OPTIMUM study, an RCT comparing ponesimod with teriflunomide in adult patients with active RMS. The study is not relevant for the benefit assessment because teriflunomide is not an ACT for the present research question. The company did not verify the suitability of the OPTIMUM study for an indirect comparison with the ACT.

Results

The company did not submit any suitable data for assessing the added benefit of ponesimod in comparison with the ACT for treatment-naive patients or for pre-treated patients or for patients without highly active RMS. Consequently, there is no hint of added benefit of ponesimod in comparison with the ACT; an added benefit is therefore not proven for this research question.

Research question 2: pre-treated patients with highly active RMS

The company did not present any data for assessing the added benefit of ponesimod in comparison with the ACT for pre-treated patients with active RMS. Consequently, there is no hint of added benefit of ponesimod in comparison with the ACT; an added benefit is therefore not proven for this research question.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the presented results, the probability and extent of added benefit of the drug ponesimod in comparison with the ACT have been assessed as follows:

Table 3 presents a summary of the probability and extent of added benefit of ponesimod.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into , categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Ponesimod – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adult patients with active RMS without any prior disease-modifying therapy or adult patients with prior disease-modifying therapy whose disease is not highly active	IFN-β 1a or IFN-β 1b or glatiramer acetate or ocrelizumab, taking into account approval status	Added benefit not proven
2	Adult RMS patients with highly active disease despite treatment with disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, appropriate (prior) treatment typically must be administered for at least 6 months. Depending on the frequency and severity of relapses as well as disability progression, the duration of disease-modifying therapy can be less than 6 months and must be justified.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; RMS: relapsing multiple sclerosis

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of ponesimod in comparison with the ACT in adult patients with active RMS.

The G-BA's specification of the ACT results in the research questions presented in Table 4.

Table 4: Research questions of the benefit assessment of ponesimod

Research question	Therapeutic indication	ACT[a]
1	Adult patients with active RMS without any prior disease-modifying therapy or adult patients with prior disease-modifying therapy whose disease is not highly active	IFN-β 1a or IFN-β 1b or glatiramer acetate or ocrelizumab, taking into account approval status
2	Adult RMS patients with highly active disease despite treatment with disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, appropriate (prior) treatment typically must be administered for at least 6 months. Depending on the frequency and severity of relapses as well as disability progression, the duration of disease-modifying therapy can be less than 6 months and must be justified.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; RMS: relapsing multiple sclerosis

In this benefit assessment, the following terminology is used for the research questions:

- Research question 1: treatment-naive patients as well as pre-treated patients and patients without highly active RMS
- Research question 2: pre-treated patients with highly active RMS

The company followed the G-BA's specification of the ACT for research question 2. For research question 1, the company departed from the G-BA's specification by identifying teriflunomide as an additional ACT option, alongside the options specified by the G-BA.

The company justified the addition of teriflunomide primarily with recommendations of national and international guidelines [3-5] as well as with the health care situation in Germany [6]. Further, the company asserted that based on the data submitted in the teriflunomide benefit dossier, there was no evidence of lesser effectiveness of teriflunomide when compared with interferon (IFN) β 1a [7].

The company's rationale is not plausible. As discussed by the company itself, the G-BA did not identify any added benefit of the drug teriflunomide in comparison with the ACT of IFN-β 1a. The study used by the G-BA for the assessment of teriflunomide did not prove the noninferiority of teriflunomide versus IFN-β 1a with regard to relapse-related outcomes [8]. Nor was the study included in the assessment designed for this purpose. In the teriflunomide assessment report, the European Medicines Agency likewise points this out [9]. Consequently, the present benefit

assessment was conducted in comparison with the ACT specified by the G-BA, disregarding the option of teriflunomide.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 12 months were used to derive added benefit. This concurs with the company's inclusion criteria.

2.3 Research question 1: treatment-naive patients as well as pre-treated patients and patients without highly active RMS

2.3.1 Information retrieval and study pool

Information retrieval

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on ponesimod (as of 13 April 2021)
- Bibliographic literature search on ponesimod (most recent search on 22 April 2021)
- Search in trial registries / study results databases on ponesimod (most recent search on 20 April 2021)
- Search on the G-BA website on ponesimod (most recent search on 10 May 2021)

To check the completeness of the study pool:

- Search in trial registries for ponesimod (most recent search on 7 July 2021); see Appendix A of the full dossier assessment for the search strategies.

The check for completeness of the study pool revealed no relevant studies for comparing ponesimod versus the ACT specified by the G-BA. The company, in contrast, identified the OPTIMUM RCT comparing ponesimod with teriflunomide [10] and used it for its assessment.

Evidence provided by the company

For research question 1, the company submitted the OPTIMUM study. This is an RCT comparing ponesimod with teriflunomide in adult patients with active RMS. The study is not relevant for the benefit assessment because teriflunomide is not an ACT for the present research question (see Section 2.2). The company's dossier does not discuss whether the benefit assessment could have used an indirect comparison of ponesimod versus the ACT specified by the G-BA on the basis of the OPTIMUM study, with teriflunomide as the common comparator.

Alongside the OPTIMUM study, Module 4 A of the company's dossier lists, for the study pool of its benefit assessment, the AC-058B201 study in the category of placebo-controlled studies. However, Module 4 A of the company's dossier subsequently fails to present any results from this study. The company also listed this study among the studies disregarded in its benefit assessment, reasoning that it is a dose-finding study. The study's publication submitted by the company shows that it is an RCT comparing 3 different dosages of ponesimod with placebo [11]. Since the AC-058B201 study does not investigate any comparison of ponesimod versus the ACT, it is irrelevant for the present benefit assessment.

2.3.2 Results on added benefit

The company did not submit any suitable data for assessing the added benefit of ponesimod in comparison with the ACT for treatment-naive patients or for pre-treated patients or for patients without highly active RMS. Consequently, there is no hint of added benefit of ponesimod in comparison with the ACT; an added benefit is therefore not proven for this research question.

2.3.3 Probability and extent of added benefit

The company did not submit any suitable data for assessing any added benefit of ponesimod in comparison with the ACT in treatment-naive patients or pre-treated patients or patients without highly active RMS. Consequently, there is no proof of added benefit of ponesimod in comparison with the ACT for research question 1.

This departs from the assessment by the company, which has derived an indication of minor added benefit for research question 1, but in comparison with teriflunomide rather than with the ACT.

2.4 Research question 2: pre-treated patients with highly active RMS

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on ponesimod (as of 13 April 2021)
- Bibliographic literature search on ponesimod (most recent search on 22 April 2021)
- Search in trial registries / study results databases on ponesimod (most recent search on 20 April 2021)
- Search on the G-BA website on ponesimod (most recent search on 10 May 2021)

To check the completeness of the study pool:

- Search in trial registries for ponesimod (most recent search on 7 July 2021); see Appendix A of the full dossier assessment for the search strategies.

No relevant study was identified from the check. The company likewise did not identify any suitable studies.

2.4.2 Results on added benefit

The company did not present any data for assessing the added benefit of ponesimod in comparison with the ACT for pre-treated patients with active RMS. Consequently, there is no hint of added benefit of ponesimod in comparison with the ACT; an added benefit is therefore not proven for this research question.

2.4.3 Probability and extent of added benefit

The company did not present any data for assessing any added benefit of ponesimod in comparison with the ACT in pre-treated patients or patients without highly active RMS. Consequently, there is no proof of added benefit of ponesimod in comparison with the ACT for research question 2.

This concurs with the company’s assessment.

2.5 Probability and extent of added benefit – summary

Table 5 presents a summary of the results of the benefit assessment of ponesimod in comparison with the ACT.

Table 5: Ponesimod – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with active RMS without any prior disease-modifying therapy or adult patients with prior disease-modifying therapy whose disease is not highly active	IFN-β 1a or IFN-β 1b or glatiramer acetate or ocrelizumab, taking into account approval status	Added benefit not proven
2	Adult RMS patients with highly active disease despite treatment with disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, appropriate (prior) treatment typically must be administered for at least 6 months. Depending on the frequency and severity of relapses as well as disability progression, the duration of disease-modifying therapy can be less than 6 months and must be justified.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IFN: interferon; RMS: relapsing multiple sclerosis

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Hemmer B. Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis-optica-Spektrum-Erkrankungen und MOG-IgG-assoziierten Erkrankungen. S2k-Leitlinie. Herausgegeben von der Kommission Leitlinien der Deutschen Gesellschaft für Neurologie. AWMF-Registernummer: 030/050 [online]. 2021 [Accessed: 18.05.2021]. URL: https://dgn.org/leitlinien/.

4. Montalban X, Gold R, Thompson AJ et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur J Neurol 2018; 25(2): 215-237. https://dx.doi.org/10.1111/ene.13536.

5. Rae-Grant A, Day GS, Marrie RA et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018; 90(17): 777-788. https://dx.doi.org/10.1212/WNL.0000000000005347.

6. Janssen-Cilag. Berechnung der Verordnungen von MS-Therapien auf DDD-Basis in Deutschland im Zeitverlauf basierend auf Daten des Wissenschaftlichen Instituts der AOK (WIdO). 2021.

7. sanofi-aventis. Dossier zur Nutzenbewertung gemäß § 35a SGB V. Teriflunomid (AUBAGIO). Modul 4 A. Schubförmig-remittierende Multiple Sklerose. Stand: 26.09.2013 [online]. 2013 [Accessed: 06.04.2021]. URL: https://www.g-ba.de/downloads/92-975-397/2013-09-26_Modul4A_Teriflunomid.pdf.

8. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Teriflunomid [online]. 2014 [Accessed: 11.08.2021]. URL: https://www.g-ba.de/downloads/40-268-2727/2014-03-20_AM-RL-XII_Teriflunomid_2013-10-01-D-078_TrG.pdf.

9. European Medicines Agency. CHMP Assessment report AUBAGIO. 27 June 2013. EMA/529295/2013 [online]. 2013 [Accessed: 23.04.2021]. URL: https://www.ema.europa.eu/en/documents/assessment-report/aubagio-epar-public-assessment-report_en.pdf.

10. Kappos L, Fox RJ, Burcklen M et al. Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study: A Randomized Clinical Trial. JAMA Neurol 2021; 78(5): 558-567. https://dx.doi.org/10.1001/jamaneurol.2021.0405.

11. Olsson T, Boster A, Fernandez O et al. Oral ponesimod in relapsing-remitting multiple sclerosis: a randomised phase II trial. J Neurol Neurosurg Psychiatry 2014; 85(11): 1198-1208. https://dx.doi.org/10.1136/jnnp-2013-307282.

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