IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-62

Cladribine (multiple sclerosis) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Cladribin (multiple Sklerose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Cladribine (multiple sclerosis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
30 November 2017

Internal Commission No.:
A17-62

Address of publisher:
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Keywords: cladribine, multiple sclerosis, benefit assessment

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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
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN-β	interferon beta
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
SGB	Sozialgesetzbuch (Social Code Book)
SPMS	secondary progressive multiple sclerosis

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 cladribine. Assessment was based on a dossier of the company. The dossier was sent to IQWiG on 30 November 2017.

Research question

The aim of the present report is to assess the added benefit of cladribine in comparison with the appropriate comparator therapy (ACT) in adult patients with highly active relapsing remitting multiple sclerosis (RRMS) defined by clinical procedures or imaging techniques.

The G-BA differentiated between 3 patient groups in its specification of the ACT in the approved therapeutic indication. Three research questions resulted from this for the assessment; their therapeutic indications and ACTs are presented in Table 2.

Table 2: Research questions of the benefit assessment of cladribine in adult patients with highly active RRMS

Research question	Subindication	ACT[a]
1	Patients with RRMS who have not yet received disease-modifying therapy	**IFN-β 1a or 1b** or glatiramer acetate under consideration of the approval
2	Patients with RRMS with highly active disease despite treatment[b] with a disease-modifying therapy	Alemtuzumab or **fingolimod** or natalizumab or, if indicated, change within the basic therapeutic agents (IFN-β 1a or 1b or glatiramer acetate under consideration of the approval)
3	Patients with secondary progressive multiple sclerosis (SPMS) with superimposed relapses	**IFN-β 1a or 1b**

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months and has to be justified.
G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

The company followed the ACT specified by the G-BA and, from the possible options, chose IFN-β 1a or 1b for research questions 1 and 3, and fingolimod for research question 2.

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

Results for research questions 1 and 3

No data are available for the assessment of the added benefit of cladribine in comparison with the ACT for patients with RRMS who have not yet received disease-modifying therapy (research question 1) and patients with SPMS with superimposed relapses (research question 3). An added benefit is therefore not proven.

Results for research question 2

The company presented no RCT on the direct comparison of cladribine with the ACT for patients with RRMS with highly active disease despite treatment with a disease-modifying therapy (research question 2). Since the company identified no RCTs of direct comparison, it conducted an indirect comparison of cladribine versus fingolimod with placebo as common comparator. The study pool of the company comprises the CLARITY study on the comparison of cladribine with placebo. For the comparison of fingolimod with placebo, the company identified the studies FREEDOMS and FREEDOMS II.

Only patients with highly active disease despite treatment with disease-modifying therapy are relevant for research question 2. The company presented post-hoc analyses of the CLARITY study for this patient group. This subpopulation comprised a total of 102 participants. 46 participants of this subpopulation received cladribine and 56 participants received placebo. For fingolimod, data on the relevant subpopulation (from the FREEDOMS and FREEDOMS II studies) can be found in the publications Derfuss 2015 and Devonshire 2012. The Derfuss 2015 publication comprises analyses of the relevant subpopulation on the basis of both studies, i.e. FREEDOMS and FREEDOMS II. Data of a total of 506 participants of the studies (N = 249 fingolimod and N = 257 placebo) were included in the analyses. The publication Devonshire 2012 comprises a further analysis which is exclusively based on data from the FREEDOMS study (N = 84 fingolimod and N = 80 placebo). Altogether, these patients represent the subpopulation relevant for the present research question.

For the adjusted indirect comparison of cladribine versus fingolomid, the company presented results only for the outcomes of the category morbidity (annualized relapse rate, disability progression [confirmed over 3 months], disability progression [confirmed over 6 months] and new or newly enlarged T2 lesions). However, the company derived no added benefit of cladribine for any of these outcomes.

The company presented no data for the research questions from the categories of mortality, health-related quality of life and side effects, since the publications Derfuss 2015 and Devonshire 2012 do not comprise analyses from the studies FREEDOMS / FREEDOMS II for these outcome categories. Thus, particularly the data on side effects were completely missing for the assessment. Hence, balancing of benefit and harm of the treatment options is not

possible. The data on the indirect comparison presented by the company were thus unsuitable to draw conclusions on the added benefit of cladribine versus the ACT. Moreover, the similarity of the populations of the study CLARITY and the studies FREEDOMS / FREEDOMS II is questionable.

The adjusted indirect comparison presented by the company was therefore unsuitable to derive conclusions on the added benefit of cladribine in comparison with the ACT specified by the G-BA for the relevant patient population in research question 2. An added benefit for this population is therefore not proven.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug cladribine compared with the ACT is assessed as follows:

It can be concluded from the available data that an added benefit of cladribine versus the ACT specified by the G-BA is not proven for any of the 3 patient groups.

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

[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 4 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: Cladribine – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Patients with RRMS who have not yet received disease-modifying therapy	**IFN-β 1a or 1b** or glatiramer acetate under consideration of the approval	Added benefit not proven
2	Patients with RRMS with highly active disease despite treatment[b] with a disease-modifying therapy	Alemtuzumab or **fingolimod** or natalizumab or, if indicated, change within the basic therapeutic agents (IFN-β 1a or 1b or glatiramer acetate under consideration of the approval)	Added benefit not proven
3	Patients with SPMS with superimposed relapses	IFN-β 1a or 1b	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months and has to be justified.
G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

The G-BA decides on the added benefit.

2.2 Research questions of the dossier assessment

The aim of the present report is to assess the added benefit of cladribine in comparison with the appropriate comparator therapy (ACT) in adult patients with highly active relapsing remitting multiple sclerosis (RRMS) defined by clinical procedures or imaging techniques.

The G-BA differentiated between 3 patient groups in its specification of the ACT in the approved therapeutic indication. Three research questions resulted from this for the assessment; their therapeutic indications and ACTs are presented in Table 4.

Table 4: Research questions of the benefit assessment of cladribine in adult patients with highly active RRMS

Research question	Subindication	ACT[a]
1	Patients with RRMS who have not yet received disease-modifying therapy	**IFN-β 1a or 1b** or glatiramer acetate under consideration of the approval
2	Patients with RRMS with highly active disease despite treatment[b] with a disease-modifying therapy	Alemtuzumab or **fingolimod** or natalizumab or, if indicated, change within the basic therapeutic agents (IFN-β 1a or 1b or glatiramer acetate under consideration of the approval)
3	Patients with SPMS with superimposed relapses	**IFN-β 1a or 1b**

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months and has to be justified.
G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

The company followed the ACT specified by the G-BA and, from the possible options, chose IFN-β 1a or 1b for research questions 1 to 3, and fingolimod for research question 2.

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

2.3 Research question 1: Patients with RRMS who have not yet received disease-modifying therapy

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on cladribine (status: 4 October 2017)
- bibliographical literature search on cladribine (last search on 4 October 2017)
- search in trial registries for studies on cladribine (last search on 4 October 2017)
- bibliographical literature search on the ACT (last search on 4 October 2017)
- search in trial registries for studies on the ACT (last search on 4 October 2017)

To check the completeness of the study pool:

- search in trial registries for studies on cladribine (last search on 19 December 2017)

In its dossier, the company presented no relevant study on research question 1. Nor was a relevant study identified from the check of the completeness.

Placebo-controlled studies presented by the company

In its dossier, the company presented the placebo-controlled approval studies CLARITY [3] and CLARITY EXTENSION [4]. It used analyses of the relevant subpopulation (patients with RRMS who had not yet received disease-modifying therapy) for the derivation of the added benefit. However, the data presented by the company are unsuitable to derive an added benefit of cladribine in comparison with the ACT, because these studies do not include control groups in which the patients are treated with the ACT (see Section 2.7.2.3.2 of the full dossier assessment).

2.3.2 Results on added benefit

The company presented no relevant data for the assessment of the added benefit of cladribine in comparison with the ACT for patients with RRMS who had not yet received disease-modifying therapy. This resulted in no hint of an added benefit of cladribine in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of cladribine in comparison with the ACT in patients with RRMS who have not yet received disease-modifying therapy, an added benefit of cladribine is not proven for these patients.

This does not concur with the company's assessment. The company stated that, due to the lack of studies, it was not possible to prove an added benefit of cladribine in comparison with the ACT in the direct or in the indirect comparison on the basis of RCTs. Nevertheless, the company derived a hint of a non-quantifiable added benefit based on the placebo-controlled approval studies CLARITY [3] and CLARITY EXTENSION [4] (see Section 2.7.2.3.2 of the full dossier assessment).

2.3.4 List of included studies

Not applicable as the company presented no data for research question 1 that are relevant for the benefit assessment.

2.4 Research question 2: Patients with RRMS despite treatment with disease-modifying therapy

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on cladribine (status: 4 October 2017)
- bibliographical literature search on cladribine (last search on 4 October 2017)
- search in trial registries for studies on cladribine (last search on 4 October 2017)
- bibliographical literature search on the ACT (last search on 21 September 2017)
- search in trial registries for studies on the ACT (last search on 2 October 2017)

To check the completeness of the study pool:

- search in trial registries for studies on cladribine (last search on 19 December 2017)
- bibliographical literature search on the ACT (last search on 8 January 2018)
- search in trial registries for studies on the ACT (last search on 5 January 2018)

The company presented no RCT on the direct comparison of cladribine with the ACT for patients with RRMS with highly active disease despite treatment with a disease-modifying therapy. No relevant RCT was identified from the check of the completeness of the study pool. Nor was an additional relevant study identified from the check of the completeness of the study pool presented by the company for the indirect comparison with fingolimod.

Placebo-controlled studies presented by the company

In its dossier, the company presented the placebo-controlled approval studies CLARITY [3] and CLARITY EXTENSION [4]. It used analyses of the relevant subpopulation (patients with RRMS despite treatment with a disease-modifying therapy) for the derivation of the added benefit. However, the data presented by the company were unsuitable to derive an added benefit of cladribine in comparison with the ACT (see Section 2.7.2.3.2 of the full dossier assessment).

Study pool of the company for the indirect comparison

Since the company identified no RCTs of direct comparison, it conducted an indirect comparison according to Bucher [5] of cladribine versus fingolimod with placebo as common comparator.

The adjusted indirect comparison presented by the company was unsuitable to derive conclusions on the added benefit of cladribine in comparison with the ACT specified by the G-BA for the relevant patient population in research question 2. This is justified below. For this purpose, at first the studies used by the company are described.

The study pool of the company for the indirect comparison comprises the CLARITY study on the comparison of cladribine with placebo. For the comparison of fingolimod with placebo, the company identified the studies FREEDOMS [6] and FREEDOMS II [7].

Table 9 and Table 10 (in Appendix A of the full dossier assessment) describe the studies CLARITY, FREEDOMS and FREEDOMS II presented by the company for the indirect comparison.

Study on cladribine

The CLARITY study is a multicentre, randomized, double-blind, placebo-controlled phase 3 study. The diagnosis of multiple sclerosis had to be made using the McDonald criteria revised in 2005. The patients should have had at least one documented relapse in the previous year. The baseline value on the Expanded Disability Status Scale (EDSS) had to range between 0 and 5.5 at the start of the study. Previous treatment with one disease-modifying therapy before the start of the study was permitted, however, this therapy should not have been performed during the last 3 months before the start of the study. Lack of effectiveness of 2 or more previous disease-modifying therapies (except of treatment failure due to intolerance) was another exclusion criterion for study inclusion.

The study had a 3-arm design. In 2 treatment arms, the patients received 3.5 mg/kg or 5.25 mg/kg cladribine once daily (oral administration) on 4 or 5 subsequent days in week 1 and week 5 of the respective treatment year (year 1 and 2). The treatment arm with 5.25 mg/kg cladribine daily will not be considered further because this dosage is not approved [8]. The patients of the 3rd treatment arm received placebo. The treatment duration was 96 weeks.

Primary outcome of the study was the relapse rate after a treatment duration of 48 and 96 weeks; secondary outcomes were other relapse-related outcomes, disability progression, disability severity, health-related quality of life and AEs.

A total of 870 patients were randomly assigned to the 2 relevant study arms (N = 433 patients to the cladribine arm and 437 patients to the placebo arm).

The company presented post-hoc analyses of the patients with highly active RMMS despite treatment with a disease-modifying therapy. In accordance with the European Medicines Agency (EMA) approval, high disease activity was operationalized as at least one relapse in the year before the start of the study, and, at the start of the study, either at least one gadolinium-enhancing T1-lesions or at least 9 T2 lesions despite progress-modifying therapy, or 2 relapses in the year before the start of the study despite progress-modifying treatment. This subpopulation comprised a total of 102 participants. 46 participants of this subpopulation received cladribine and 56 participants received placebo. Altogether, these patients represented the subpopulation of the CLARITY study relevant for the present research question.

Studies on fingolimod

The studies FREEDOMS and FREEDOMS II were multicentre, randomized, double-blind, placebo-controlled studies. The designs of the studies were identical. Adult patients with RRMS were enrolled. The diagnosis of multiple sclerosis had to be made using the McDonald criteria revised in 2005. The patients should have had at least one documented relapse in the previous

year or 2 documented relapses in the 2 previous years. At the start of the study, the baseline value on the EDSS had to be between 0 and 5.5. Regarding pretreatment with IFN-β, the limitation was that patients were excluded who had received IFN-β treatment within the last 3 months before randomization.

Both studies had a 3-arm design. In 2 treatment arms, the patients received 0.5 mg or 1.25 mg fingolimod respectively (oral administration) once daily. In the third treatment arm, the patients received placebo once daily. Only the dosage of 0.5 mg daily is approved for fingolimod [9]; therefore, the treatment arms with 1.25 mg fingolimod daily will not be considered further. The treatment duration was 24 months in total.

In the FREEDOMS study, a total of 843 patients were randomly assigned to the 2 relevant study arms (N = 425 patients to the fingolimod arm and N = 418 patients to the placebo arm). In the FREEDOMS II study, a total of 713 patients were randomly assigned to the 2 relevant study arms (N = 358 patients to the fingolimod arm and N = 355 patients to the placebo arm).

Primary outcome of both studies was the annualized relapse rate; secondary outcomes were other relapse-related outcomes, disability progression, disability severity, health-related quality of life and AEs.

Only patients with highly active disease despite treatment with disease-modifying therapy were relevant for the present research question. Data on the relevant subpopulation are found in the publications Derfuss 2015 [10] and Devonshire 2012 [11]. Both publications defined highly active RRMS as at least 1 relapse in the year before the start of the study, and, at the start of the study, either at least one gadolinium-enhancing T1-lesion or at least 9 T2 lesions or at least just as much relapses in the year before baseline as in the previous year. The Derfuss 2015 publication comprises analyses of the relevant subpopulation on the basis of data from both studies, i.e. FREEDOMS and FREEDOMS II. Data of a total of 506 participants of the studies (N = 249 fingolimod and N = 257 placebo) were included in the analyses. The publication Devonshire 2012 comprises an analysis which is exclusively based on data from the FREEDOMS study (N = 84 fingolimod and N = 80 placebo). Altogether, these patients represented the subpopulation relevant for the present research question.

Reasons for the lack of suitability of the indirect comparison presented by the company

No data on the outcome categories "side effects", "mortality" and "health-related quality of life"

For the adjusted indirect comparison of cladribine versus fingolomid, the company presented results only for the outcomes of the category morbidity (annualized relapse rate, disability progression [confirmed over 3 months], disability progression [confirmed over 6 months] and new or newly enlarged T2 lesions). However, the company derived no added benefit of cladribine from any of these outcomes.

The company presented no data on the outcomes of other categories, because the publications Derfuss 2015 [10] and Devonshire 2012 [11] do not comprise relevant analyses. Particularly the data on side effects were thus completely missing for the assessment. Hence, balancing of benefit and harm of the treatment options is not possible. The data on the indirect comparison presented by the company were thus unsuitable to draw conclusions on the added benefit of cladribine versus the ACT.

Similarity of the study populations questionable

The similarity of the populations of the study CLARITY and the studies FREEDOMS / FREEDOMS II is questionable:

- The patient characteristics at the start of the study regarding "time since diagnosis" as well as "overall volume of the T2 lesions" differ significantly between the study populations. The patients of the FREEDOMS / FREEDOMS II studies are characterized by shorter disease durations (about 9.5 years in the CLARITY study vs. about 6.3 years in the FREEDOMS / FREEDOMS II studies) and a significantly lower overall volume of the T2 lesions (about 15 cm^3 in the CLARITY study vs. about 6.3 cm^3 in the FREEDOMS / FREEDOMS II studies) (see Table 11, Appendix A of the full dossier assessment).
- Moreover, differences in the results of the placebo arms of the studies included contradict a similarity of the studies (see Table 12, Appendix A of the full dossier assessment). This applies particularly to the outcome "annual relapse rate" in the subpopulation of the patient group pretreated with IFN-β. The G-BA recommended subgroup analyses after pre-treatment for research question 2. Data for this subpopulation are only available from the FREEDOMS study (Devonshire 2012 [11]). The annual relapse rate of the patient group pretreated with IFN-β of the FREEDOMS study was almost twice as high as that of the patient group of the CLARITY study (0.37 in the placebo arm of the CLARITY study vs. 0.63 in the placebo arm of the FREEDOMS study) (see Table 12).
- A significant difference between the placebo arms was also observed for the outcome "number of new or newly enlarged T2 lesions". The patients of the studies FREEDOMS and FREEDOMS-II recorded an increase of new or newly enlarged T2 lesions (3.91 in the placebo arm of the CLARITY study vs. 9.58 in the placebo arm of the FREEDOMS and FREEDOMS-II studies) that was more than twice as high than that of the CLARITY study (see Table 12, Appendix A of the full dossier assessment).

The similarity of the study populations included in the indirect comparison is altogether questionable.

Summary

The company submitted no direct comparative studies on cladribine versus the ACT. The data on the indirect comparison presented by the company were thus unsuitable to draw conclusions on the added benefit of cladribine versus the ACT.

Hence, overall, no evaluable data were available for the derivation of the added benefit of cladribine in comparison with the ACT.

2.4.2 Results on added benefit

Usable data for the assessment of the added benefit of cladribine for patients with RRMS with highly active disease despite treatment with a disease-modifying therapy are missing. This resulted in no hint of an added benefit of cladribine in comparison with the ACT; the added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The data presented by the company for the assessment of the added benefit of cladribine in patients with RRMS with highly active disease despite treatment with a disease-modifying therapy are unsuitable for the derivation of an added benefit. Hence, an added benefit of cladribine is not proven for these patients.

This does not concur with the company's assessment. The company stated that, due to the lack of studies, it was not possible to prove an added benefit of cladribine in comparison with the ACT in the direct comparison on the basis of RCTs. It further explained that an added benefit of cladribine vs. the ACT fingolimod could not be proved for the outcomes used by it in the indirect comparison presented either. Nevertheless, the company derived a hint of a non-quantifiable added benefit based on the placebo-controlled approval studies CLARITY [3] and CLARITY EXTENSION [4] (see Section 2.7.2.3.2 of the full dossier assessment).

2.4.4 List of included studies

Not applicable as the company presented no data for research question 2 that are relevant for the benefit assessment.

2.5 Research question 3: Patients with SPMS with superimposed relapses

2.5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on cladribine (status: 4 October 2017)
- bibliographical literature search on cladribine (last search on 4 October 2017)
- search in trial registries for studies on cladribine (last search on 4 October 2017)
- bibliographical literature search on the ACT (last search on 4 October 2017)
- search in trial registries for studies on the ACT (last search on 4 October 2017)

To check the completeness of the study pool:

- search in trial registries for studies on cladribine (last search on 19 December 2017)
- In its dossier, the company presented no relevant study on research question 3. Nor was a relevant study identified from the check of the completeness.

2.5.2 Results on added benefit

The company presented no data for the assessment of the added benefit of cladribine in comparison with the ACT for patients with SPMS with superimposed relapses. This resulted in no hint of an added benefit of cladribine in comparison with the ACT. An added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of cladribine in comparison with the ACT in patients with RRMS with superimposed relapses, an added benefit of cladribine is not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for this patient group.

2.5.4 List of included studies

Not applicable as the company presented no data for research question 3 that are relevant for the benefit assessment.

2.6 Probability and extent of added benefit – summary

Table 5: Cladribine – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Patients with RRMS who have not yet received disease-modifying therapy	**IFN-β 1a or 1b** or glatiramer acetate under consideration of the approval	Added benefit not proven
2	Patients with RRMS with highly active disease despite treatment[b] with a disease-modifying therapy	Alemtuzumab or **fingolimod** or natalizumab or, if indicated, change within the basic therapeutic agents (IFN-β 1a or 1b or glatiramer acetate under consideration of the approval)	Added benefit not proven
3	Patients with SPMS with superimposed relapses	IFN-β 1a or 1b	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Adequate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on the disability progression, treatment with a disease-modifying therapy might take less than 6 months and has to be justified.
G-BA: Federal Joint Committee; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

The assessment described above deviates from that of the company, which claims a non-quantifiable medical added benefit each for patients with RRMS who have not yet received disease-modifying therapy (research question 1) and for patients with RRMS with highly active disease despite treatment with a disease-modifying therapy (research question 2). The company did not claim an added benefit for patients with SPMS with superimposed relapses (research question 3).

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. 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.

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