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Diroximel fumarate (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 *Diroximelfumarat (multiple Sklerose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 2022). 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.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Jutta Scheiderbauer and one other person.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier 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
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN	interferon
Ig	immunoglobulin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
SD	standard deviation
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 diroximel fumarate. 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 3 January 2022.

Research question

The aim of the present report is to assess the added benefit of diroximel fumarate in comparison with the appropriate comparator therapy (ACT) in adults with relapsing remitting multiple sclerosis (RRMS) who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of diroximel fumarate

Therapeutic indication	ACT[a]
Adults with RRMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy[b]	**IFN-β1a** or IFN-β1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab, taking into account approval status

a. Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.
b. Taking into account the drug properties of diroximel fumarate, adults with highly active RRMS despite treatment with disease-modifying therapy are not considered to be the target population of diroximel fumarate.

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

The company followed the G-BA's specification of the ACT and chose interferon (IFN)-β1a as ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 12 months are used for the derivation of the added benefit.

Results

Concurring with the company, the check of the completeness of the study pool identified no randomized controlled trial (RCT) that would allow a direct comparison of diroximel fumarate against IFN-β1a, the ACT option chosen by the company.

In the absence of studies of direct comparisons, the company conducted an information retrieval for further investigations with diroximel fumarate and thereby identified the single-arm study EVOLVE-MS-1. Since this study did not have a comparator arm, the company aimed to compare individual arms of different studies using propensity score matching based on individual patient data for the comparison with IFN-β1a. The company was able to identify 7 studies (5 studies on IFN-β1a and 2 studies on pegylated IFN-β1a). Of these studies, the company considered 2 (the ADVANCE study and the DECIDE study) to be potentially relevant, but only considered the DECIDE study (IFN-β1a) for the comparison using propensity score matching. The company's approach is not appropriate. Due to the exclusion of the ADVANCE study (and possibly other studies), the study pool of the company is potentially incomplete. The results from the comparison of the 2 studies EVOLVE-MS-1 and DECIDE presented by the company are therefore not used for the assessment of the added benefit.

In addition, there are further points of criticism:

- The 2 studies EVOLVE-MS-1 and DECIDE used different operationalizations for the outcome of relapses. It is therefore conceivable that relapses were documented less frequently in the EVOLVE-MS-1 study than in the DECIDE study due to additionally defined criteria.
- It cannot be assessed whether the company identified and considered all relevant confounders for propensity score matching.
- The methods for the propensity score procedure of the company is not described in such a way that the different steps of the applied procedure can be understood in sufficient detail. Furthermore, there are no sensitivity analyses with different propensity score procedures. However, such sensitivity analyses are necessary to demonstrate the best possible structural equality of the analysis populations for the chosen propensity score procedure.

No suitable data are available to assess the added benefit of diroximel fumarate in comparison with IFN-β1a as ACT in adults with RRMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy. This results in no hint of added benefit of diroximel fumarate in comparison with IFN-β1a as ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of the probability and extent of added benefit of diroximel fumarate.

[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

Table 3: Diroximel fumarate – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with RRMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy[b]	**IFN-β1a** or IFN-β1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab, taking into account approval status	Added benefit not proven

a. Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.
b. Taking into account the drug properties of diroximel fumarate, adults with highly active RRMS despite treatment with disease-modifying therapy are not considered to be the target population of diroximel fumarate.

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

The G-BA decides on the added benefit.

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].

2.2 Research question

The aim of the present report is to assess the added benefit of diroximel fumarate in comparison with the ACT in adults with RRMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of diroximel fumarate

Therapeutic indication	ACT[a]
Adults with RRMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy[b]	**IFN-β1a** or IFN-β1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab, taking into account approval status

a. Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.
b. Taking into account the drug properties of diroximel fumarate, adults with highly active RRMS despite treatment with disease-modifying therapy are not considered to be the target population of diroximel fumarate.

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

The company followed the G-BA's specification of the ACT and chose IFN-β1a as ACT.

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

2.3 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 lists on diroximel fumarate (status: 12 October 2021)
- bibliographical literature search on diroximel fumarate (last search on 12 October 2021)
- search in trial registries/trial results databases for studies on diroximel fumarate (last search on 12 October 2021)
- search on the G-BA website for diroximel fumarate (last search on 12 October 2021)
- study list on the ACT (without information on status)
- bibliographical literature search on the ACT (last search on 25 October 2021)

- search in trial registries/trial results databases for studies on the ACT (last search on 29 October 2021)
- search on the G-BA website for the ACT (last search on 18 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on diroximel fumarate (last search on 17 January 2022); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCT that would allow a direct comparison of diroximel fumarate against IFN-β1a, the ACT option chosen by the company.

In the absence of studies of direct comparisons, the company conducted an information retrieval for further investigations with diroximel fumarate. This information retrieval identified the single-arm diroximel fumarate study EVOLVE-MS-1 [3,4].

Since the EVOLVE-MS-1 study did not have a comparator arm, the company aimed to compare individual arms of different studies using propensity score matching for the comparison with IFN-β1a. For the information retrieval of further investigations with IFN-β1a, the company therefore specified that individual patient data had to be available. As the company was unable to identify any studies based on these criteria, it subsequently checked whether the company itself had any studies on IFN-β1a in the therapeutic indication for which individual patient data were available. With this approach, the company was able to identify 7 studies (5 studies on IFN-β1a and 2 studies on pegylated IFN-β1a). Of these studies, the company considered 2 (the ADVANCE study and the DECIDE study) to be potentially relevant, but only considered the DECIDE study (IFN-β1a) [5,6] for the comparison using propensity score matching.

The company's approach is not appropriate. The data presented from the comparison of individual arms of different studies cannot be used for the benefit assessment. This is explained below.

Evidence provided by the company

Study with diroximel fumarate (EVOLVE-MS-1)

The EVOLVE-MS-1 study is a single-arm, open-label and multicentre study. It included adults with RRMS who had either previously completed a 5-week study of diroximel fumarate and dimethyl fumarate (EVOLVE-MS-2 [7]) (referred to as "rollover" patients in the study) or patients without prior treatment with diroximel fumarate (referred to as "de novo" patients in the study). Patients had to be between 18 and 65 years old and diagnosed with RRMS according to the revised McDonald criteria of 2010 [8]. In addition, patients had to be neurologically stable with no signs of relapse within 30 days prior to starting treatment and have an Expanded Disability Status Scale (EDSS) score of 6.0 or less.

A total of 1057 patients were included in the study (rollover: 464 patients, of which 239 patients with previous treatment with diroximel fumarate; de novo: 593 patients). Treatment with diroximel fumarate was given for up to 96 weeks. The study recorded different outcomes of the outcome categories of morbidity and health-related quality of life, and adverse events (AEs).

Study pool on IFN-β1a potentially incomplete

For the comparator side, the company identified several studies with IFN-β1a for which individual patient data were available to the company. These are listed in Table 5.

Table 5: List of the studies of the company with IFN-β1a and available individual patient data as well as reasons for exclusion of the company for further consideration to carry out a comparison of individual arms from different studies

Study	**Interventions**	**Study duration Study period (years)**	**Reasons for exclusion of the company[a]**
MSCRG-IFN-β1a approval study	IFN-β1a (Avonex) vs. placebo	Study duration: 104 weeks Patient inclusion since: 1990[b]	Study period[c]
CHAMPS	IFN-β1a (Avonex) vs. placebo	Study duration: 156 weeks Study period: 1996–2000	Study population[d] Study period[c]
Extension study CHAMPIONS	IFN-β1a (Avonex)	Study duration: 521 weeks Study period: 2001–2003	Study population[d] Study design[e] Study period[c]
Dose comparison study (European IFN-1a [Avonex] dose comparison study)	IFN-β1a (Avonex)	Study duration: 156 weeks Patient inclusion since: 1996[b]	Study population[d] Study design[e] Study period[c]
DECIDE	IFN-β1a (Avonex) vs. daclizumab	Study duration: 96–144 weeks Study period: 2010–2014	Not applicable
ADVANCE	Pegylated IFN-β1a (Plegridy) vs. placebo	Study duration: 96 weeks Study period: 2009–2013	Not applicable
ATTAIN	Pegylated IFN-β1a (Plegridy)	Study duration: 96–104 weeks Study period: 2011–2015	Study design[e]

a. The company's reasons for exclusion are based on the criteria defined by the company according to Table 4-41 in Module 4 A [9].
b. According to the company, an exact end of the study period could not be identified. However, the company assumes that the study was completed before 2011.
c. Exclusion criterion of the company: study period before 2011.
d. Exclusion criterion of the company: study population outside the therapeutic indication.
e. Exclusion criterion of the company: extension studies without maintaining RCT conditions, dose-reduction and comparison studies, non-interventional studies, systematic reviews, meta-analysis.

IFN: interferon; MSCRG: Multiple Sclerosis Collaborative Research Group; RCT: randomized controlled trial

The company checked these studies against the additional inclusion/exclusion criteria defined by the company for an indirect comparison using the propensity score procedure (see Module 4 A Table 4-41 [9]) for further consideration. These criteria are partly comprehensible (e.g. only consideration of the approved population in the therapeutic indication), partly not sufficiently justified (exclusion of studies completed before 2011) or questionable (exclusion of extension studies without maintaining RCT conditions for an intended propensity score

procedure). The exclusion of studies that were completed well before 2011 seems plausible in principle, e.g. due to the changed diagnostic criteria for multiple sclerosis (MS) over time. The company excluded the studies MSCRG IFN-β1a, CHAMPS and CHAMPIONS as well as a dose comparison study and the ATTAIN study on the basis of the 3 criteria of study population, study design and study period (see also Table 5). The company's selection cannot be verified, as no further information on these studies is available in the dossier.

Based on the inclusion/exclusion criteria defined by the company for conducting an indirect comparison, only the studies DECIDE and ADVANCE were assessed as potentially suitable by the company. In the DECIDE study, IFN-β1a was administered, and in the ADVANCE study, pegylated IFN-β1a. Of these 2 studies, the company only used the DECIDE study for the comparison of individual arms of different studies. In its dossier, the company provided references for IFN-β1a only for the DECIDE study. The dossier contains no documents on the ADVANCE study; the information provided by the company on the ADVANCE study can therefore not be verified.

The DECIDE study is a multicentre, double-blind RCT comparing IFN-β1a with daclizumab in patients with RRMS. It included adults aged 18 to 55 years whose RRMS was diagnosed using the 2005 McDonald criteria [10]. In addition, patients had to have active disease, which was defined as 2 or more clinical relapses within the previous 3 years with at least one clinical relapse in the 12 months prior to randomization, or one or more clinical relapses and one or more new magnetic resonance imaging (MRI) lesions within the previous 2 years with at least one of these events in the 12 months prior to randomization. In addition, an EDSS of no more than 5.0 was required.

A total of 1841 patients were assigned in a ratio of 1:1 to the 2 treatment arms. Treatment with IFN-β1a or daclizumab was for a maximum period of 96 to 144 weeks. Primary outcome of the study was the annualized relapse rate. Secondary outcomes were further morbidity outcomes and side effects.

The company justified its selection of the DECIDE study on the one hand by stating that a robust comparability for a meta-analytical summary of both studies cannot be ensured due to differences in efficacy, safety, pharmacology and galenics of the substances IFN-β1a and pegylated IFN-β1a. On the other hand, the company argued that a higher number of patients were treated in the IFN-β1a arm of the DECIDE study than in the pegylated IFN-β1a arm of the ADVANCE study (922 patients versus 512 patients).

The exclusion of the ADVANCE study is not appropriate. According to the G-BA's specification of the ACT for the drug IFN-β1a, all finished medicinal products are to be taken into account, irrespective of the form and frequency of application, as none of the medicinal products is generally preferable to the other [11]. Thus, the ADVANCE study, where, in contrast to the DECIDE study, the pegylated form of IFN-β1a was administered, is also potentially relevant to the present benefit assessment. In the course of the intended propensity

score procedure, it would therefore have been appropriate and necessary to consider all patients of the relevant studies.

Overall, due to the exclusion of the ADVANCE study (and possibly other studies such as ATTAIN), the study pool of the company is potentially incomplete. The results from the comparison of the 2 studies EVOLVE-MS-1 and DECIDE presented by the company are not used for the assessment of the added benefit.

Further points of criticism

Regardless of the potentially incomplete study pool, there are further points of criticism. These are described below.

Different operationalizations for the outcome of relapses in the 2 studies EVOLVE-MS-1 and DECIDE

In the present data situation of comparing individual arms from different studies, the operationalizations of the outcomes included in the assessment have to be sufficiently similar between the studies considered.

The studies EVOLVE-MS-1 and DECIDE defined the outcome of relapses as new or recurrent neurological symptoms not associated with fever or infection, and lasting at least 24 hours. In the DECIDE study, the symptoms had to be additionally confirmed by new objective neurological findings upon examination by an independent examining neurologist. In the EVOLVE-MS-1 study, on the other hand, criteria were defined that provided for the inclusion of the EDSS. Neurological symptoms were only considered to be a relapse if, in addition to the general relapse definition, at least one of the following criteria applied:

- new objective neurological findings that, as assessed by the treating neurologist, are functionally consistent with the findings on the EDSS (performed within 7 days of symptom onset) and are associated with an increase of 0.5 points in the total score from the previous visit
- increase in score by ≥ 2 points in any functional system of the EDSS other than changes in bladder function and cognition
- increase in score by ≥ 1 point in 2 functional systems of the EDSS other than changes in bladder function and cognition

Overall, it is thus evident that the operationalizations of the outcome of relapses differ between the 2 studies. Due to the additionally defined criteria in the EVOLVE-MS-1 study, it is conceivable that relapses were documented less frequently in this study than in the DECIDE study.

Confounder identification for propensity score matching

Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies, group differences in possible confounders, i.e. factors that are related to both the treatment and outcomes and can thus alter a treatment effect, must be taken into account in the effect estimation. The first prerequisite for this is that relevant confounders are systematically identified. In addition, the underlying procedure for identifying the confounders must be sufficiently documented.

In the identification of confounders, the company first referred to a review of the use and quality of propensity score methods in the therapeutic indication of MS by Karim 2020 [12], which cites the confounders most frequently considered in the underlying studies. In the Karim 2020 review, the time period for the search for studies was limited to the years 2013 to 2018. The company therefore updated the information retrieval to include the period from 2018 and identified 24 additional publications. In addition, the company listed the subgroups most frequently used in the benefit assessment procedures from 2011 to 2021 in the therapeutic indication of MS as well as possible effect modifiers according to the report plan of *Alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab and teriflunomide for the treatment of adult patients with highly active relapsing remitting multiple sclerosis* [13]. The company made a selection from the identified confounders and submitted these to one clinical expert for validation.

The company's approach is not appropriate. There is no information in the company's dossier on how the Karim 2020 review was identified. Consequently, it is also unclear whether the procedure of the company is suitable for the systematic identification of relevant confounders. Furthermore, in Karim 2020, as in the company's information retrieval, only the term "propensity score" was searched for. This severely limits the information retrieval for observational studies, which can be important sources for identifying the relevant confounders. In addition, the company only named the most frequently used effect modifiers of the previous benefit assessment procedures in the therapeutic indication of MS. It did not provide any information on the cut-off value it took into account. The company did not address effect modifiers that were identified in previous benefit assessment procedures but were considered less frequently. Neither did it cite these in Module 4 A, nor did it argue why they were not considered in the present procedure. Overall, it can therefore not be assessed whether the company identified and considered all relevant confounders.

Propensity score procedure

For the comparison of diroximel fumarate (EVOLVE-MS-1) with IFN-β1a (DECIDE), the company used 1:1 greedy matching without imputation and a caliper value of 0.2 of the pooled standard deviation (SD) of the logit of the propensity score. Although the company mentioned general advantages of this procedure, it did not provide any reasons why other procedures are less suitable in the present case. Furthermore, there are no sensitivity analyses with different propensity score procedures. However, such sensitivity analyses are necessary to demonstrate

the best possible structural equality of the analysis populations for the chosen propensity score procedure.

Overall, the company did not describe the methods in Module 4 A in such a way that the different steps of the applied propensity score procedure can be understood in sufficient detail. With the exception of the source code, Module 5 also provided no further information on the methods. Thus, it cannot be assessed whether the methods used by the company were determined without prior knowledge of the data.

In addition, there are further specific aspects:

- The company did not provide any information in Module 4 A on the fact that the caliper value for the propensity score matching was subsequently adjusted for the efficacy population according to the source code in order to achieve an adequate matching of the patients with regard to the confounder "age".
- In the source code for propensity score matching, the company named the variable "Baseline Normalized Brain Volume" as a confounder, but did not take it into account in the matching. Module 4 A of the dossier did not mention this variable as possible confounder.
- According to information provided in Module 4 A, the company used a population of patients who have received at least one dose of diroximel fumarate or IFN-β1a for the analyses of both the benefit and the harm outcomes. In the source code, however, 2 populations (safety and efficacy population) were matched separately using propensity scores. Thus, according to the source code, differently defined populations were used for the analyses of the respective outcomes.
- In the IFN-β1a arm of the DECIDE study, about half of the pretreated patients were already receiving IFN-β 1a. According to the inclusion criteria of the study, the patients also had to have active disease. Taking into account the 2021 S2k guideline for diagnosis and treatment of MS, neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein (MOG) immunoglobulin (Ig)G-associated diseases [14], a change in therapy is indicated for such patients. In addition, the IFN-β1a arm of the DECIDE study also included patients with highly active disease (22%) who are not comprised by the research question investigated, provided they were pretreated patients. No information is available on this combined proportion. The company did not exclude those patients who are not comprised by the research question. It is unclear what the final proportion of these is in the matched population used for the analyses.

2.4 Results on added benefit

No suitable data are available to assess the added benefit of diroximel fumarate in comparison with IFN-β1a as ACT in adults with RRMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy.

This results in no hint of added benefit of diroximel fumarate in comparison with IFN-β1a as ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 6 summarizes the result of the assessment of added benefit of diroximel fumarate in comparison with the ACT.

Table 6: Diroximel fumarate – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with RRMS who have not yet received disease-modifying therapy, or adults with non-highly active disease pretreated with disease-modifying therapy[b]	**IFN-β1a** or IFN-β1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab, taking into account approval status	Added benefit not proven

a. Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.
b. Taking into account the drug properties of diroximel fumarate, adults with highly active RRMS despite treatment with disease-modifying therapy are not considered to be the target population of diroximel fumarate.

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

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable, at least considerable added benefit on the basis of its data provided.

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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