IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Dimethylfumarat – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 July 2014). 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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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Arnfin Bergmann, Practice Dr Bergmann, Neuburg, Germany

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.

IQWiG employees involved in the dossier assessment[2]:

- Sebastian Werner
- Ralf Bender
- Dorothea Gechter
- Andreas Gerber-Grote
- Florina Kerekes
- Corinna Kiefer
- Sarah Mostardt
- Katrin Nink
- Sibylle Sturtz
- Beate Wieseler
- Min Zhou

Keywords: dimethyl fumarate, multiple sclerosis – relapsing-remitting, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DMF	dimethyl fumarate
GA	glatiramer acetate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLMM	generalized linear mixed model
IFN-β1a	interferon beta-1a
IFN-β1b	interferon beta-1b
IM	intramuscular
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NICE	National Institute for Health and Care Excellence
RRMS	relapsing remitting multiple sclerosis
SC	subcutaneous
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 dimethyl fumarate. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 30 April 2014.

Research question

The aim of this report is to assess the added benefit of dimethyl fumarate (DMF) in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsing remitting multiple sclerosis (RRMS).

The G-BA specified the ACT for this therapeutic indication as follows: beta-interferon (1a or 1b) or glatiramer acetate (GA).

The company chose interferon beta-1a (IFN-β1a) from the options specified by the G-BA, but limited its choice to IFN-β1a 44µg subcutaneous (SC) (Rebif), one of the preparations with this drug. According to the G-BA's specification at drug level, all IFN-β1a preparations have to be considered irrespective of the form of administration, i.e. also an additional preparation with this drug – IFN-β1a, 30 µg intramuscular (IM) (Avonex). This approach did not influence the company's study pool for the direct comparison (no direct comparative studies available). However, the company presented an indirect comparison on the comparison of DMF versus the ACT (IFN-β1a), which was incomplete with regard to content as a consequence of the limitation of the comparator therapy.

The present benefit assessment was conducted in comparison with the ACT IFN-β1a.

The assessment was conducted based on patient-relevant outcomes.

Results

Direct comparison

There were no direct comparative studies on DMF versus the ACT IFN-β1a.

Indirect comparison

The company presented a network meta-analysis on the indirect comparison of DMF versus IFN-β1a, 44 µg SC (Rebif) in Module 4 of the dossier. For this purpose, the company searched for a network of DMF, IFN-β1a (SC and IM), IFN-β1b, GA, and placebo. A total of 14 studies were included in the network meta-analysis. This study pool contained treatment arms with DMF, IFN-β1a, IFN-β1b, GA, and placebo. The various preparations with the drug IFN-β1a (SC [Rebif] and IM [Avonex]) and their possible dosages (44 µg and 22 µg SC [Rebif]) were considered separately in the network.

However, the indirect comparison presented is unsuitable to draw conclusions on the added benefit of DMF versus IFN-β1a for the following reasons:

- The indirect comparison is incomplete with regard to content.
- The statistical model used for the network meta-analysis is unsuitable.
- The 3 basic assumptions of network meta-analyses – similarity, homogeneity and consistency – were not adequately checked by the company. Moreover, the similarity of the studies included is doubtful.

Indirect comparison incomplete with regard to content

Although the network in principle allows the comparison of DMF versus the ACT as a whole (IFN-β1a in all forms of administration), the company presented exclusively results on the comparison of DMF versus IFN-β1a, 44 µg SC (Rebif) in Module 4 of the dossier, and hence only partially represented the ACT (IFN-β1a). The indirect comparison presented is therefore incomplete with regard to content.

Network meta-analyses were based on an unsuitable statistical model

The network meta-analyses were conducted on the basis of generalized linear mixed models [GLMMs]) modelling the treatment effect as fixed effect and the study effect as random effect in the GLMMs presented. Modelling the study as random effect can lead to cross-level bias (also called ecological bias) and to an underestimation of the standard errors to such a degree that these become smaller than in a meta-analytical model with exclusively fixed effects. The network meta-analyses presented were therefore not based on an adequate statistical model.

Unsuitable check of similarity, homogeneity and consistency

The 3 basic assumptions of network meta-analyses – similarity, homogeneity and consistency – were not adequately checked by the company.

To check the assumption of similarity, the company conducted a qualitative comparison of the study methods and of the characteristics of the patient populations of the studies included. The company inferred from this consideration that the studies included in the indirect comparison essentially have comparable study populations (as well as comparable methods). This assessment was not followed. For example, the large range of the proportions of patients

with at least one relapse in the placebo arms of the studies included (39% to 84%) is an aspect against the similarity of the studies. Moreover, on the basis of the patient characteristics "pretreatment", "severity and previous duration of disease" and "previous relapse activity", no sufficient similarity of the study populations included in the network meta-analysis can be assumed. Contrary to the company's assessment, the assumption of similarity was therefore violated.

The company checked homogeneity by using correlation and regression analyses to identify potential effect modifiers. This approach is unsuitable. Moreover, the check of the assumption of consistency was also inadequate because no criteria were named for the violation of the assumptions of consistency and the check was only conducted for 2 selected comparisons and was therefore incomplete.

Summary

No suitable data were available for assessing the added benefit of DMF versus the ACT, neither for a direct comparison nor for an indirect comparison.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

Table 2: Dimethyl fumarate – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with relapsing remitting multiple sclerosis	**Beta interferon (1a** or 1b) or glatiramer acetate	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**. In the present case, the company limited the ACT to beta interferon 1a 44 µg SC (Rebif). This limitation was not followed. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SC: subcutaneous		

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

[4] 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), see [1]. 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, no added benefit, or less benefit), see [2].

2.2 Research question

The aim of this report is to assess the added benefit of DMF in comparison with the ACT in adult patients with RRMS.

For this therapeutic indication, the G-BA specified the following ACT:

- beta-interferon (1a or 1b) or glatiramer acetate

The company chose IFN-β1a from the options specified by the G-BA, but limited its choice to IFN-β1a 44µg SC (Rebif) [3], one of the preparations with this drug. Due to the selection criteria, the search designed to find direct comparative studies of DMF and Rebif would not identify studies with the other preparation with this drug – IFN-β1a, 30 µg IM (Avonex [4])[5]. According to the G-BA's specification at drug level, all IFN-β1a preparations have to be considered irrespective of the form of administration. This approach did not influence the company's study pool for the direct comparison (no direct comparative studies available). However, the company presented an indirect comparison on the comparison of DMF versus the ACT (IFN-β1a), which was incomplete with regard to content as a consequence of the limitation of the comparator therapy (see Section 2.3 and Section 2.7.1 of the full dossier assessment).

The present benefit assessment was conducted in comparison with the ACT IFN-β1a.

The assessment was conducted based on patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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[6]:

- study list on DMF (studies completed up to 7 January 2014)
- bibliographical literature search on DMF (last search on 16 January 2014)
- search in trial registries for studies on DMF (last search on 2 December 2013)
- bibliographical literature search on DMF, the ACT as well as IFN-β1b and GA (indirect comparison, last search on 12 December 2013)
- search in trial registries for studies on DMF, the ACT as well as IFN-β1b and GA (indirect comparison, last search on 2 December 2013)

[5] The search for the indirect comparison presented was not limited to Rebif.

[6] The relevant time point for the search was the market entry in Germany on 1 March 2014.

To check the completeness of the study pool:

- search in trial registries for studies on DMF (last search on 16 May 2014)

The data presented by the company were unsuitable to draw conclusions on the added benefit of DMF versus the ACT. This is justified below.

Direct comparison

There were no direct comparative studies on DMF versus the ACT IFN-β1a.

Indirect comparison

The company presented a network meta-analysis on the indirect comparison of DMF versus IFN-β1a, 44 µg SC (Rebif) in Module 4 of the dossier.

For this purpose, the company searched for a network of DMF, IFN-β1a (SC and IM), IFN-β1b, GA, and placebo. A total of 14 studies were included in the network meta-analysis (DEFINE [5], CONFIRM [6], BECOME [7,8], BEYOND [9], Bornstein [10], Calabrese [11], Copolymer 1 MS [12,13], Etemadifar [14], EVIDENCE [15,16], IFNB MS [17-19], INCOMIN [20], MSCRG [21,22], PRISMS [23,24] and REGARD [25]). This study pool contained treatment arms with DMF, IFN-β1a, IFN-β1b, GA, and placebo. The various preparations with the drug IFN-β1a (SC [Rebif] and IM [Avonex]) and their possible dosages (44 µg and 22 µg SC [Rebif]) were considered separately in the network (see Section 2.7.2.1 of the full dossier assessment).

Table 3 shows the available pairwise direct comparisons of interventions of the included studies (see Section 2.7.2.3.2 of the full dossier assessment for further characteristics of all studies).

Table 3: Pairwise direct comparisons of interventions (intervention 1 [columns] vs. intervention 2 [rows]) of the studies included in the network meta-analysis

Interventions	**DMF**	**IFN-β1a, 22 µg, SC (Rebif)**	**IFN-β1a, 44 µg, SC (Rebif)**	**IFN-β1a, 30 µg (Avonex)**	**IFN-β1b, 250 µg, SC**	**GA**	**Placebo**
DMF		–	–	–	–	*CONFIRM*	*DEFINE CONFIRM*
IFN-β1a, 22 µg, SC (Rebif)	–		*PRISMS*	–	–	–	*PRISMS*
IFN-β1a, 44 µg, SC (Rebif)	–	PRISMS		*EVIDENCE Calabrese Etemadifar*	*Etemadifar*	*REGARD Calabrese*	*PRISMS*
IFN-β1a, 30 µg, IM (Avonex)	–	–	EVIDENCE Calabrese Etemadifar		*Etemadifar INCOMIN*	*Calabrese*	*MSCRG*
IFN-β1b, 250 µg, SC	–	–	Etemadifar	Etemadifar INCOMIN		*BEYOND BECOME*	*IFNB MS*
GA	CONFIRM	–	REGARD Calabrese	Calabrese	BEYOND BECOME		*CONFIRM Bornstein Copolymer*
Placebo	DEFINE CONFIRM	PRISMS	PRISMS	MSCRG	IFNB MS	CONFIRM Bornstein Copolymer	

–: no direct comparison available; DMF: dimethyl fumarate; GA: glatiramer acetate; IFN-β; beta interferon; IM: intramuscular; SC: subcutaneous; vs.: versus

However, the indirect comparison presented is unsuitable to draw conclusions on the added benefit of DMF versus the ACT for the following reasons:

- The indirect comparison is incomplete with regard to content.
- The statistical model used for the network meta-analysis is unsuitable.
- The 3 basic assumptions of network meta-analyses – similarity, homogeneity and consistency – were not adequately checked by the company. Moreover, the similarity of the studies included is doubtful.

These deficiencies are described in detail below.

Indirect comparison incomplete with regard to content

Although the network in principle allows the comparison of DMF versus the ACT as a whole (IFN-β1a in all forms of administration), the company presented exclusively results on the comparison of DMF versus IFN-β1a, 44 µg SC (Rebif) in Module 4 of the dossier, and hence only partially represented the ACT (IFN-β1a). The indirect comparison presented is therefore incomplete with regard to content.

Network meta-analyses were based on an unsuitable statistical model

The network meta-analyses were conducted on the basis of GLMMs. Similar models are also used in the literature [26] and are recommended in the National Institute for Health and Care Excellence (NICE) technical support documents as SAS implementation [27]. In the GLMMs presented, however, the treatment effect was modelled as fixed effect, and the study effect as random effect. Jones et al. [26] explicitly stated that, when using GLMMs, the study itself is not to be modelled as random effect but the treatment effects within the studies. Modelling the study as random effect can lead to cross-level bias (also called ecological bias). Jones et al. [26] referred to Whitehead [28], which emphasized that the study should not be modelled as random effect. This can lead to an underestimation of the standard errors to such a degree that these become smaller than in a meta-analytical model with exclusively fixed effects. An underestimation of the standard errors is equivalent to confidence intervals that are too narrow and can lead to treatment effects wrongly assessed as statistically significant. The network meta-analyses presented were therefore not based on an adequate statistical model.

Unsuitable check of similarity, homogeneity and consistency

The 3 basic assumptions of network meta-analyses – similarity, homogeneity and consistency – were not adequately checked by the company.

To check the assumption of similarity, the company conducted a qualitative comparison of the study methods and of the characteristics of the patient populations of the studies included. The patient characteristics were compared with one another both at the level of the individual study arms and after summarizing the arms of different studies with the same intervention. The company inferred from this consideration that the studies included in the indirect comparison essentially have comparable study populations (as well as comparable methods). This assessment was not followed. For example, the large range of the proportions of patients with at least one relapse in the placebo arms of the studies included (39% to 84%) is an aspect against the similarity of the studies (see Table 4). The evaluation of IQWiG to check the similarity of the studies included on the basis of the characteristics of the study populations is presented in Section 2.7.2.3.2 of the full dossier assessment. Overall, in addition to the different proportions of patients with relapse in the placebo arms of the studies, on the basis of the patient characteristics “pretreatment”, “severity and duration of disease” and “previous relapse activity”, no sufficient similarity of the study populations included in the network meta-analysis can be assumed. Contrary to the company’s assessment, the assumption of similarity was therefore violated (see Section 2.7.2.3.2 of the full dossier assessment).

Table 4: Proportion of patients with at least one relapse in the placebo arms of the placebo-controlled studies in the network meta-analysis

Study treatment	Study duration	Placebo	
		N	Patients with event n (%)
Studies with dimethyl fumarate			
DEFINE	96 weeks	408	171 (42)
CONFIRM	96 weeks	363	140 (39)
Studies with beta interferon			
PRISMS (IFN-β1a [Rebif])	2 years	187	157 (84)
MSCRG (IFN-β1a [Avonex])	2 years	87[a]	64 (74)
IFNB MS (IFN-β1b)	2 years	112[b]	94 (84)
Studies with glatiramer acetate			
Copolymer 1 MS	2 years	126	92 (73)
Bornstein	2 years	23	17 (74)

a: Analysis of the patients who entered the study sufficiently early to be observed at the date of analysis 104 weeks; randomized patients in the placebo arm: 143.
b: Analysis of the first 338 patients (all study arms) after 2 years; randomized patients in the placebo arm: 123.
IFN-β: beta interferon; N: number of analysed patients; n: number of patients with event

The company checked homogeneity by using correlation and regression analyses to identify potential effect modifiers. This approach is unsuitable. First the degree of heterogeneity has to be described before potential effect modifiers are searched. All pairwise meta-analyses of the relevant network have to be used for this. Inferring homogeneity from the non-significance of potential effect modifiers in correlation and regression analyses is inadequate. Hence the company's approach to check homogeneity was inadequate.

The company principally assumes consistency in the network. A check of the assumption of consistency was conducted using a qualitative comparison of the estimates from the network meta-analysis and the corresponding direct comparison. No criteria for violation of the assumption of consistency were mentioned. Moreover, this check was only conducted for 2 selected comparisons and was therefore incomplete. Hence the company's approach to check consistency was inadequate.

Summary

The company submitted no direct comparative studies on DMF versus the ACT.

The data on the indirect comparison presented by the company were unsuitable to draw conclusions on the added benefit of DMF versus the ACT. According to its research question, the company only presented analyses for one preparation of the ACT (IFN-β1a, 44 µg SC [Rebif]) in Module 4 of its dossier. An adequate indirect comparison would have to be conducted versus the ACT IFN-β1a (all preparations). The studies necessary for this were contained in the company's network, but the corresponding analyses were not presented. The

indirect comparison presented is incomplete with regard to content. Moreover, because of the methodological flaws of the network meta-analysis presented (unsuitable statistical model and unsuitable check of similarity, homogeneity and consistency), overall the corresponding results could not be used. Moreover, the assumption of similarity of the studies included was violated. Overall, no valid conclusions on added benefit of DMF versus the ACT can be drawn on the basis of the network meta-analysis presented. Hence there are no suitable data for the assessment of the added benefit of DMF.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

No suitable data were available for assessing the added benefit of DMF, neither for a direct comparison nor for an indirect comparison. Hence the added benefit of DMF versus the ACT is not proven.

This result deviates from the company's assessment, which derived an added benefit on the basis of the results of the indirect comparison presented.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of DMF in comparison with the ACT is shown in Table 5.

Table 5: Dimethyl fumarate – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with relapsing remitting multiple sclerosis	**Beta interferon (1a** or 1b) or glatiramer acetate	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**. In the present case, the company limited the ACT to beta interferon 1a 44 µg SC (Rebif). This limitation was not followed. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SC: subcutaneous		

This assessment deviates from that of the company, which derived an indication of considerable added benefit of DMF in comparison with IFN-β1a 44 µg SC (Rebif) on the basis of relapse-related outcomes.

The G-BA decides on the added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

Not applicable as no studies were included in the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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