IQWiG Reports – Commission No. A14-33

Addendum to Commission A14-14 (dimethyl fumarate)[1]

Addendum

Commission: A14-33
Version: 1.0
Status: 25 September 2014

[1] Translation of addendum A14-33 *Addendum zum Auftrag A14-14 (Dimethylfumarat)* (Version 1.0; Status: 25 September 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Addendum to Commission A14-14 (dimethyl fumarate)

Commissioning agency:
Federal Joint Committee

Commission awarded on:
8 September 2014

Internal Commission No.:
A14-33

Address of publisher:
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

IQWiG employees involved in the addendum[2]:

- Beate Wieseler
- Corinna Kiefer

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

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

Table of contents

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN-β1a	interferon beta-1a
IM	intramuscular
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MTC	Mixed Treatment Comparison
SC	subcutaneous

1 Background

On 8 September 2014 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-14 (benefit assessment of dimethyl fumarate [1]).

In the commenting procedure on the assessment of dimethyl fumarate, in its comment from 22 August 2014 and in the oral hearing conducted on 8 September 2014, the pharmaceutical company (hereinafter abbreviated to "the company") submitted supplementary information to the G-BA that went beyond the information in the dossier [2]. These were further analyses on the indirect comparison of dimethyl fumarate and interferon beta-1a (IFN-β1a).

The G-BA commissioned IQWiG with the assessment of the analyses submitted under consideration of the information provided in the dossier. The data were to be assessed under the research question of whether, under consideration of the analyses submitted by the company, the indirect comparison allows to draw conclusions on the added benefit of dimethyl fumarate versus the appropriate comparator therapy (ACT).

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Additional documents provided by the company

The indirect comparison presented in the company's dossier from 28 April 2014 was unsuitable for conclusions on the added benefit of dimethyl fumarate versus IFN-β1a, which the company had chosen from the alternative ACTs specified by the G-BA, for the following reasons (for more details, see dossier assessment [1]):

- The indirect comparison was incomplete with regard to contents because of the limitation to the subcutaneous administration form of IFN-β1a.
- The statistical model used for the network meta-analysis was unsuitable.
- The 3 basic assumptions of network meta-analyses – similarity, homogeneity and consistency – were not adequately checked by the company. Moreover, the studies included were not sufficiently similar.

In its comment on the dossier assessment, the company addressed these 3 reasons with the following additional documents:

- results of an indirect comparison of dimethyl fumarate versus IFN-β1a 30 µg, intramuscular (IM), and versus the pooled analysis of the administration forms of IFN-β1a (30 µg IM and 44 µg, subcutaneous [SC])
- supplementary analyses on the indirect comparison with additional analyses on the statistical model of the network meta-analysis as well as on the investigation of homogeneity consistency and similarity of the studies in the network

In the following sections, the newly submitted documents are assessed under the research question of whether conclusions on the added benefit of dimethyl fumarate can be drawn from the indirect comparison of dimethyl fumarate and IFN-β1a.

2.2 Completeness with regard to content of the indirect comparison of dimethyl fumarate and IFN-ß1a

In its dossier from 28 April 2014, the company only presented results on the comparison of dimethyl fumarate versus IFN-ß1a 44 µg SC (Rebif) in its indirect comparison. It did not consider the second available administration form IFN-ß1a 30 µg IM (Avonex) and hence only partially presented the ACT (IFN-β1a). The indirect comparison presented was therefore incomplete with regard to content.

In its comment, the company presented an indirect comparison of dimethyl fumarate versus the complete study pool of IFN-β1a (both administration forms). However, this is still unsuitable for drawing conclusions on the added benefit of dimethyl fumarate versus IFN-β1a for the following reasons:

- The results of the indirect comparison of dimethyl fumarate and "the pooled analysis of IFN-β1a" could not be used because, for the calculation, the company still used the statistical model of the network meta-analysis it had already employed in the dossier. As already explained in detail in the dossier assessment, this model is inadequate [1]. Furthermore, no investigation of the underlying assumptions of the network meta-analysis was performed for the results from the pooled analysis of IFN-β1a. Such an investigation was only available for the networks from the dossier, in which IFN-β1a 44 µg SC and IFN-β1a 30 µg IM were included separately.
- Not all available patient-relevant outcomes were considered in the indirect comparison of dimethyl fumarate versus IFN-β1a (both administration forms). For some outcomes, the company justified this by claiming that no corresponding data on the ACT IFN-β1a 30 µg IM were available in the study publications included. This justification cannot be followed for all outcomes mentioned because the clinical study report (CSR) of the MSCRG study with IFN-β1a 30 µg IM was available to the company, which was the sponsor of this study. The CSR contained results on individual relevant adverse events, for example. Moreover, the company presented no analysis on serious adverse events without justifying this. The CSR of the MSCRG study also contained results for this outcome.
- The analysis of deaths presented within the indirect comparison of dimethyl fumarate versus IFN-β1a (both administration forms) was incomplete because it did not consider the information on deaths (one death under IFN-β1a), which was also available in the CSR on the MSCRG study.

2.3 Suitability of the statistical models of the network meta-analysis presented

The company submitted "additional analyses on the statistical model" in its comment [2]. It presented a comparison of the results of its statistical model of the network meta-analysis it had already submitted in the dossier with the results of a new network meta-analysis model, which also only considered the comparison of dimethyl fumarate and IFN-β1a 44 µg SC (Rebif) for most outcomes. In addition, the company presented 2 measures of goodness-of-fit. It claimed that the new model was an analysis suggested by IQWiG. The company regarded its results presented in the dossier from 28 April 2014 as confirmed because both models showed a statistically significant advantage of dimethyl fumarate versus IFN-β1a 44 µg SC in relapse rate, and also because the measures of goodness-of-fit showed a better goodness-of-fit for the model already used in the dossier.

Since for most outcomes, the company again compared dimethyl fumarate only with IFN-β1a 44 µg SC (Rebif) and not with both administration forms of IFN-β1a, this indirect comparison was also incomplete with regard to contents and unsuitable to draw conclusions on the added benefit of dimethyl fumarate versus IFN-β1a (both administration forms).

There are additional aspects of the company's explanations that were not accepted. The statistical model of the network meta-analysis used in the dossier was unsuitable, as was already justified in detail in the dossier assessment [1]. A key reason was the potential

underestimation of the standard error up to smaller values than in a fixed-effect model [3]. The company claimed in its comment that the statistical model it used in the dossier was a model that was well described in the international literature, but cited no specific sources. The company's references only referred to general publications on indirect comparisons. However, the criticism of the model used by the company in the dossier did not refer to network meta-analysis models in general, but specifically to the modelling of the study as random effect.

In its comment, the company also submitted results based on a newly adapted network meta-analysis model. It claimed that this was an analysis suggested by IQWiG. This is incorrect because no specific model was mentioned in the dossier assessment. It was only shown that the modelling of the study as random effect was inadequate and a publication [4] was referred to, which emphasized that the treatment effects within the studies, i.e. the interactions between treatment and study, should be modelled as random effect.

The results of the revised network meta-analysis presented by the company were also unsuitable to investigate the added benefit of dimethyl fumarate. Even though the company claimed in its comment that it had included both the main effects treatment and study as fixed effects and the interaction between these 2 main effects as random effect in the new model, it is clear from the corresponding source code that this was not the case. According to the source code, the company included an interaction between treatment and study as random effect in the model, but completely left out the main effect of the study from the model. The newly submitted results from the comment were therefore based on a model with treatment as fixed effect and the interaction of treatment and study as random effect. The main effect of the study was missing in the model. This is inadequate because this model was therefore based on the assumption that the average probabilities of events were the same in all studies. Hence the company did not adequately address the criticism in the dossier assessment of the statistical model of the network meta-analysis submitted in the dossier so that the results could not be used. Instead, the company could have used an established method for the calculation of network meta-analyses, such as the Bayesian Mixed Treatment Comparison (MTC) meta-analysis [5] the company itself cited, or the free netmeta package [6] for the R software [7], which is based on graph theory methods [8]. The publication by Jones 2011 [4] cited several times within the dossier assessment recommends a network meta-analysis model with symmetry restrictions and names an SAS source code, which could have been used too.

In addition, the company claimed that its network meta-analysis model originally submitted in the dossier showed a better goodness-of-fit than the model calculated for the comment. This argument is irrelevant because the goodness-of-fit of different models can only be compared among the models of adequate content. Better goodness-of-fit alone is insufficient for the choice of a model. Contrary to the company's claim, this approach was also not recommended by IQWiG or in the publication by Jones 2011 [4].

Moreover, data input into the revised network meta-analysis model was examined using the outcome "proportion of patients with relapse after 24 months" as an example. Minor inconsistencies between the results of the individual studies presented in Module 4 of the dossier and the data actually included in the model were detected. Neither the dossier nor the comment contained information on these differences. It therefore remained unclear whether they were caused by different populations used (e.g. randomized and analysed patients), for example.

2.4 Examination of the assumptions of similarity, homogeneity and consistency

With its comment, the company submitted further analyses to address the criticism in the dossier assessment of the investigation of the underlying assumptions of the network meta-analysis. However, these new analyses cannot be used because they were not available for the correct ACT, but only for the networks in which IFN-β1a 44 µg SC and IFN-β1a 30 µg IM were included separately. Apart from this primary reason, there were additional reasons for all analyses as to why these cannot be used. More details on these reasons are provided below.

2.4.1 Assumption of similarity

Based on study results in the placebo arms and on patient characteristics in the studies included, the dossier assessment concluded that no sufficient similarity of the studies included in the indirect comparison can be assumed [1]. The company addressed this result in the comment with analyses on the assumption of similarity.

The company presented "additional analyses on similarity" in Appendix II of its comment. On the one hand, it presented results from different unifactorial and multifactorial analyses to identify covariables with statistically significant influence. On the other hand, it reported effect estimations for pairwise comparisons with dimethyl fumarate after adjustment for certain covariables. However, the results were only available on the basis of the network meta-analysis model that was originally submitted in the dossier. As already explained in the dossier assessment, this is no adequate statistical model [1].

Irrespective of the reasons stated above, the analyses submitted could only be used to a limited extent anyway. The assessment of similarity should be based primarily on content criteria. The results of the analyses of covariables, as conducted by the company, largely depend on the choice of the covariables and are therefore subject to a preselection with regard to content, which needs to be justified. However, the investigation of the influence certain covariables have on the effect estimations could be used in certain situations (e.g. as sensitivity analysis).

There are further reasons as to why the analyses in the form presented are unsuitable:

- The analyses were only presented selectively for 2 outcomes (annualized relapse rate and disability progression after 3 months).

- The choice of the models (unifactorial or multifactorial) and of the covariables investigated was also not justified in the documents submitted. The choice of the covariables was not comprehensible. The company did not consider the pretreatment of the patients as a covariable, for example, although in the dossier it identified an interaction for the comparison of dimethyl fumarate with placebo and therefore a potential effect modification by pretreatment. Furthermore, the choice of models and covariables was not performed consistently for all analyses, and was therefore selective.
- A detailed description of the statistical models underlying the results was nowhere to be found in the comment. It therefore remained unclear what exactly was presented here.

2.4.2 Assumption of homogeneity

The company presented "additional analyses on homogeneity" in Appendix II of its comment. It used the I^2 statistic to investigate the assumption of homogeneity and stated that it assumed heterogeneity between the study results for values ≥ 60%. In case of pairwise comparisons with heterogeneity, the company conducted sensitivity analyses, excluding individual studies because of aspects regarding methods or content and examining the robustness of the results of the MTC meta-analysis. However, it found a value of I^2 statistic of 60.1%, which the company itself called moderate heterogeneity, for the outcome "proportion of patients with relapse after 24 months". Contrary to its own methods, it conducted no sensitivity analysis.

The company provided no justification for its choice of the I^2 statistic and the corresponding limit of 60%. When there are only few studies, IQWiG generally uses a heterogeneity test based on Q statistic and assumes considerable heterogeneity if the p-value is below 0.2. Considering the association of the 2 statistics, a p-value of 0.2 would correspond to threshold values of 40% to 50% for the I^2 statistic. Hence the company may detect heterogeneity less often in its results. Moreover, at a I^2 value of 60.1%, the lack of a sensitivity analysis causes an increase in the uncertainty of results. Since the criteria do not deviate very much from one another however, the company's approach in this concrete aspect was not completely inadequate, but resulted in an increased uncertainty of results.

Due to the further relevant deficiencies it was not checked whether the investigation of the assumption of homogeneity was conducted completely for all possible pairwise comparisons with at least 2 studies and all outcomes.

2.4.3 Assumption of consistency

The company presented "additional analyses on consistency" in Appendix II of its comment. It compared the estimations from all direct comparisons available with the corresponding estimations under the exclusive use of indirect evidence using a statistical test with a significance level of 5%.

This methodological approach was largely accepted. However, the company stated in its comment that there were no statistically significant differences between the direct and the

indirect estimations in its results. This is untrue because there was a statistically significant difference between the direct and indirect estimations for the outcome "proportion of patients with relapse after 24 months" for 2 pairwise comparisons (IFN-β1a 44 µg SC versus placebo and IFN-β1a 30 µg IM versus placebo). These inconsistencies would have had to be addressed.

The results of this investigation cannot be used for the investigation of the added benefit of dimethyl fumarate versus IFN-β1a (both administration forms) because the model originally submitted in the dossier was used as network meta-analysis model. As already explained in the dossier assessment, this statistical model is inadequate [1].

It was not checked whether the investigation of the assumption of consistency was conducted completely for all possible pairwise comparisons with direct evidence and all outcomes because of further relevant deficiencies.

2.5 Summary

In summary, the documents submitted with the company's comment, under consideration of the information in the dossier from the indirect comparison of dimethyl fumarate and IFN-β1a, were unsuitable for drawing conclusions on the added benefit of dimethyl fumarate versus the ACT for the following reasons:

- The company used the statistical model, which was already described as unsuitable in the dossier assessment, for the network meta-analysis on the comparison of dimethyl fumarate with IFN-β1a as a whole (both forms of administration). Moreover, this analysis did not report all patient-relevant outcomes.
- The presented network meta-analyses with changed statistical models, with the exception of one outcome, compared dimethyl fumarate separately with the 2 administration forms of IFN-β1a, and are therefore unsuitable for drawing a conclusion on the added benefit versus the ACT as a whole. Moreover, the source code submitted by the company for these network meta-analyses did not correspond to the company's description of the statistical model. Instead, the source code showed that an unsuitable statistical model was used.
- The investigations of the underlying assumptions of network meta-analyses (assumption of similarity, assumption of homogeneity, assumption of consistency) were incomplete. In particular, the documents for examining the assumption of similarity were unsuitable to dispel the existing doubts from the dossier assessment concerning the assumption of similarity.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dimethylfumarat: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-14 [online]. 30 July 2014 [accessed: 23 September 2014]. (IQWiG-Berichte; Volume 231). URL: https://www.iqwig.de/download/A14-14_Dimethylfumarat_Nutzenbewertung-35a-SGB-V.pdf.

2. Biogen Idec. Stellungnahme zum IQWiG-Bericht Nr. 231: Dimethylfumarat; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-14. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/111/#tab/beschluesse im Dokument "Zusammenfassende Dokumentation"].

3. Senn S. A note regarding 'random effects'. Stat Med 2014; 33(16): 2876-2877.

4. Jones B, Roger J, Lane PW, Lawton A, Fletcher C, Cappelleri JC et al. Statistical approaches for conducting network meta-analysis in drug development. Pharm Stat 2011; 10(6): 523-531.

5. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004; 23(20): 3105-3124.

6. Rücker G, Schwarzer G, Krahn U, König J. Netmeta: network meta-analysis with R; version 0.6-0 [online]. [Accessed: 24 September 2014]. URL: http://CRAN.R-project.org/package=netmeta.

7. R Foundation for Statistical Computing. The R Project for Statistical Computing [online]. [Accessed: 24 September 2014]. URL: http://www.r-project.org/index.html.

8. Rücker G. Network meta-analysis, electrical networks and graph theory. Res Syn Meth 2012; 3(4): 312-324.