Evidence Review Group Report

Dimethyl fumarate for treating relapsing-remitting multiple sclerosis

Errata

Page 17, second paragraph

The text states:

"The ERG is aware of four cases of progressive multifocal leukoencephalopathy (PML) in patients treated with fumaric esters. [redacted] The ERG's clinical advisor stated that, if PML were confirmed as an adverse event of dimethyl fumarate, guidance for discontinuation based on lymphocyte counts would be required and that monitoring of these parameters would therefore be required in clinical practice."

Should read:

"The ERG is aware of four case reports of PML occurring in patients treated with Fumaderm (3 cases) and a compounded formulation of dimethyl fumarate and copper monoethylfumarate (1 case). To date there have been no reports of PML in the clinical trial programme or post-marketing setting of patients treated with Tecfidera. The ERG's clinical advisor stated that, if PML were confirmed as an adverse event of dimethyl fumarate, guidance for discontinuation based on lymphocyte counts would be required and that monitoring of these parameters would therefore be required in clinical practice."

Page 19, third paragraph

The text states

"Trials of fingolimod and of natalizumab which are licensed only for patients with rapidly evolving severe (RES) or highly active disease were included in the MTC. These therapies are recommended by NICE only for highly active and RES disease respectively."

Should read

"Trials of fingolimod and of natalizumab which are licensed only for patients with rapidly evolving severe (RES) and highly active disease despite treatment with a beta-interferon were included in the MTC. These therapies are recommended by NICE only for highly active disease in the case of fingolimod and RES disease in the case of natalizumab."

Page 20, final paragraph

The text states:

"However, these analyses are based on a model which utilises relative risks, rather than hazard ratios for progression outcomes and does not appear to have distributions assigned to all relevant

parameters. Attempts to clarify this resulted in a model which appeared to be based on rate ratios, which the ERG believes to be more inappropriate than relative risks. Due to limitations in the availability of data and the lack of a full probabilistic model, there is some uncertainty in the ICER for dimethyl fumarate. Despite this, when the list prices are used for all drugs, the cost-effectiveness conclusion is robust to sensitivity analyses: dimethyl fumarate is not cost-effective given a cost-effectiveness threshold of £30,000 per QALY."

Should read:

"However, these analyses are based on a model which utilises relative risks, rather than hazard ratios for progression outcomes and does not appear to have distributions assigned to all relevant parameters. Attempts to clarify this resulted in a model based on hazard ratios. This model has not been used for the base case, but comparative results based on the use of the relative risk and hazard ratio have been provided as an additional document for circulation to the committee. Due to limitations in the availability and statistical methods used to estimate outcomes and the lack of a full probabilistic model, there is some uncertainty in the ICER for dimethyl fumarate."

Page 23, second paragraph

The text states

"Patients who are eligible for current DMTs (i.e. two clinically significant relapses in the previous two years for beta-interferons and glatiramer acetate)"

Should read

"Patients who are eligible for current DMTs (i.e. normally two clinically significant relapses in the previous two years for beta-interferons and glatiramer acetate)"

Page 23, fourth paragraph

The text states:

"However the ERG is aware of case reports of PML occurring in patients treated with fumaric esters including dimethyl fumarate. It is unclear whether this risk is related to how these patients were managed."

Should read:

"The ERG is aware of four case reports of PML occurring in patients treated with Fumaderm (3 cases) and a compounded formulation of dimethyl fumarate and copper monoethylfumarate (1 case). To date there have been no reports of PML in the clinical trial programme or post-marketing setting of patients treated with Tecfidera."

Page 27, first paragraph

The following text should be added to the end of the first pargraph

The guideline also states that in certain other circumstances where the evidence for efficacy is less secure, neurologists may also consider advising treatment after discussion with the patient concerning the risks and benefits. For example (i) patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes (i.e.

development of multiple sclerosis) and (ii) patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity (i.e meet the revised McDonald criteria for MS)

Page 28, first paragraph

The text states

"This criterion is different to UK prescribing guidelines for current DMT, which states that patients should have had ≥2 relapses in the preceding two years."

Should read

"This criterion is different to UK prescribing guidelines for current DMT, which states that patients should normally have had ≥2 relapses in the preceding two years"

Page 38, Table 6

Proportion of female patients should read:

	DEFINE			CONFIRM			
	Dimethyl fumarate 240mg BID	Dimethyl fumarate 240mg TID	Placebo	Dimethyl fumarate 240mg BID	Dimethyl fumarate 240mg TID	Placebo	Glatiramer acetate 20mg OD
Females: N (%)	296(72)	306(74)	306(75)	245(68)	250(72)	251(69)	247(71)

Page 42, penultimate paragraph

The text states:

The CONFIRM study showed a non-statistically significant benefit of dimethyl fumarate compared to placebo for the secondary outcome of disability progression confirmed at three months (HR 0.79, 95% CI 0.51 to 1.19).[1] The pre-planned sensitivity analysis for disability progression sustained for six months showed a hazard ratio of 0.62 (95% CI 0.37 to 1.03).

Should read:

"The CONFIRM study showed a non-statistically significant benefit of dimethyl fumarate compared to placebo for the secondary outcome of disability progression confirmed at three months (HR 0.79, 95% CI 0.51 to 1.19). The pre-planned sensitivity analysis for disability progression sustained for six months showed a hazard ratio of 0.62 (95% CI 0.37 to 1.03).[1]"

[1] figure taken from CSR: fig 20 in submission shows 0.62 (0.38, 1.00)

Page 44, Table 8

Proportion of patients relapsed by prior and no prior treatment should read:

			Proportion of patients relapsed for dimethyl fumarate vs placebo: HR (95%CI)	
Prior MS treatment				
No prior treatment			0.37 (0.24 to 0.57)	
Prior treatment			0.65 (0.45 to 0.89)	

Page 45, second paragraph

The text states

"The indication for which fingolimod is recommended by NICE (TA254) is narrower than this licensed indication."

Should read

"The indications for which fingolimod and natalizumab are recommended by NICE (TA254 and TA 127 respectively) are narrower than this licensed indication."

Page 45, Table 9

Should read

	ARR for dimethyl fumarate vs placebo: rate ratio (95% CI)	Disability progression confirmed at 3 months for dimethyl fumarate vs placebo: HR (95% CI)
Group approximating highly active disease (fingolimod indication) (n=318)	[redacted]	[redacted]
Group approximating RES disease (natalizumab indication) (n=93)	[redacted]	[redacted]

Page 45, second paragraph

The text states

[redacted]

Should read

[redacted]

Page 50, Table 14

Freedoms II - *The table states* " Mean/median disease duration 41.4". *Should read* "10.4"

Knobler 1993 - *The table states* "Relapses in previous 2 years (mean or median) Betaferon NR, Placebo 4". S*hould read* "Betaferon 4, Placebo 2.3"

MSRCG - *The table states* "Relapses in previous 2 years (mean or median) 2.3" *Should read* "NR"

TRANSFORMS - *The table states* "Percentage female currently 65.7". Should read 65.4

Page 57, first paragraph

The text states

"As previously noted, fingolimod and natalizumab are licensed and recommended by NICE for subgroups of RRMS patients who meet the following criteria".

Should read

"As previously noted, fingolimod and natalizumab are licensed only for patients with rapidly evolving severe (RES) and highly active disease despite treatment with a beta-interferon. They are recommended by NICE for subgroups who meet the following criteria:"

Page 57, first paragraph

The text states

"Although UK prescribing guidelines indicate that treatment should only be started for patients who have had ≥2 relapses in the previous two years"

Should read

"although UK prescribing guidelines indicate that treatment should normally be started for patients who have had ≥2 relapses in the previous two years

Page 60, first paragraph

The text states:

"Risk ratios are asymmetric and this has been demonstrated to be capable of generating anomalous results in an indirect comparison. However, some confusion remained regarding the effectiveness outcome for disability progression which, like other binomial outcomes, looked as though it had been modelled as a risk ratio, despite being referred to as a hazard ratio. Following ERG queries the manufacturer provided new code and results pertaining to disability progression. The new results were presented as hazard ratios although it is not clear that the code/analysis is appropriate as time does not appear to be included in the model. Given that hazard ratios represent instantaneous risk over the study time period it is unclear to the ERG that these outcomes can be modelled without the element of time. It is the opinion of the ERG that either the code supplied is incorrect or the outcomes modelled are in fact rate ratios. The ERG considers risk ratios or hazard ratios to be preferable to rate ratios for this analysis. Due to this lack of clarity the ERG have opted to use the base case results and model in the manufacturer's submission, which used a risk ratio."

Should read:

"Risk ratios are asymmetric and this has been demonstrated to be capable of generating anomalous results in an indirect comparison. However, some confusion remained regarding the effectiveness outcome for disability progression which, like other binomial outcomes, looked as though it had been modelled as a risk ratio, despite being referred to as a hazard ratio. Following ERG queries the manufacturer provided new code and results pertaining to disability progression. The new results were presented as hazard ratios although it is not clear that the code/analysis produces the most robust outcomes given the assumptions underpinning the analysis. The ERG considers that both the relative risk and the hazard ratio are uncertain. The ERG have opted to use the base case results and model in the manufacturer's submission, which used a risk ratio and present comparative results using the hazard ratio in an addendum. It is hoped that this will allow some of the uncertainty surrounding the robustness of the disease progression outcome to be highlighted."

Page 61, Table 15

The table states: Natlizumab 1.53 (1.23 to 1.91). *Should read:* 1.54 (1.23 to 1.91)

Page 62, first paragraph

The text states:

"In response to queries raised by the ERG the manufacturer supplied a revised network. This appeared to give rate ratios rather than hazard ratios."

Should read:

"In response to queries raised by the ERG the manufacturer supplied a revised network. This was based on hazard ratios."

Page 62, Table 16

The table states Teriflunomide 7mg 0.81 (0.50 to 1.23) at 3 months. *Should read* 0.81 (0.50 to 1.30)

The table states Placebo 0.67 (0.42 to 1.06) at 6 months. *Should read* 0.67 (0.42 to 1.07)

The table states Fingolimod 0.94 (0.52 to 1.71) at 6 months. *Should read* 0.95 (0.52 to 1.72)

Page 64, second paragraph

The text states "discontinuation due to any cause was lower in dimethyl fumarate groups (RR 0.75 to 0.99)."

Should state "discontinuation due to any cause was lower in dimethyl fumarate groups (RR 0.86 95% CI 0.75 to 0.99)."

Page 65, first paragraph

The text states:

The ERG is aware of four cases of progressive multifocal leukencephalopathy (PML) in patients treated with fumaric esters.[31-33]
[redacted] The ERG's clinical advisor stated that, if PML were established as an adverse effect of dimethyl fumarate, guidance for discontinuation based on lymphocyte counts would be required and that monitoring of these parameters would therefore be required in clinical practice.

Should state

"The ERG is aware of four case reports of PML occurring in patients treated with Fumaderm (3 cases) and a compounded formulation of dimethyl fumarate and copper monoethylfumarate (1 case). To date there have been no reports of PML in the clinical trial programme or post-marketing setting of patients treated with Tecfidera. The ERG's clinical advisor stated that, if PML were confirmed as an adverse event of dimethyl fumarate, guidance for discontinuation based on lymphocyte counts would be required and that monitoring of these parameters would therefore be required in clinical practice."

Page 69, first paragraph

The text states:

"Incidences of PML associated with fumaric esters have been documented;
[redacted]

Should state

"Incidences of PML associated with fumaric esters have been documented with Fumaderm (3 cases) and a compounded formulation (1 case). To date there have been no reports of PML in the clinical trial programme or post-marketing setting of patients treated with Tecfidera®.
[redacted]"

P80, Table 23

The table heading states

"Drug recommendations"

Should state

"NICE drug recommendations"

Page 87, second paragraph

The text states:

"The choice of a risk ratio over a hazard ratio maximised the number of trials included in the MTC. The manufacturer presented new analyses using what they described as a hazard ratio outcome. However, it appears that time to event data were not included in the analysis given the code provided and the outcome measure appeared to be a rate ratio instead. The ERG considers a risk ratio or a hazard ratio to be more appropriate than a rate ratio, so the rate ratio results are considered less reliable than the risk ratio results."

Should read:

""The choice of a risk ratio over a hazard ratio maximised the number of trials included in the MTC. The manufacturer presented new analyses using a hazard ratio outcome. However, it was not clear to the ERG based on the SAS code and the accompanying text that the outcome was in fact a hazard ratio; rather it was thought to be a rate ratio. This was finally confirmed as a hazard ratio, but due to the lack of clarity the relative risk base case analysis and results have been utilised throughout the report and an addendum of the comparative results obtained through the use of both the hazard ratio and relative risk outcomes provided."

Page 88, Table 29

The table states ARR Natalizumab 1.53 (1.23 to 1.91). *Should read* 1.54 (1.23 to 1.91)

Page 102, final paragraph

The text states:

"The actual price paid for other drugs including fingolimod, Avonex, Betaferon, Rebif 22µg, Rebif 44µg and glatiramer acetate by the NHS in England and Wales is less than the list price as discussed in Section 5.2.10.1. The ERG considers that a more appropriate analysis would be to evaluate the cost-effectiveness of dimethyl fumarate utilising discounted prices for every drug where possible. This is explored in Section 6."

Should read:

"The actual price paid for other drugs including fingolimod, Rebif 22µg, Rebif 44µg and glatiramer acetate by the NHS in England and Wales is less than the list price as discussed in Section 5.2.10.1. The ERG considers that a more appropriate analysis would be to evaluate the cost-effectiveness of dimethyl fumarate utilising discounted prices for every drug where possible. This is explored in Section 6."

Page 104, first paragraph

The text states:

“In the response to the points of clarifications raised by the ERG, the manufacturer provided incremental cost-effectiveness results using the hazard ratio instead of the risk ratio for 3 months sustained progression. However, it appeared to be a rate ratio rather than a hazard ratio given the code provided. This is discussed in section 4.4. The ERG considers the rate ratio results to be less reliable than the risk ratio results provided in the original submission.”

Should read:

“In the response to the points of clarifications raised by the ERG, the manufacturer provided incremental cost-effectiveness results using the hazard ratio instead of the risk ratio for 3 months sustained progression. However, results based on these additional analyses are provided in an accompanying addendum rather than the main report.”

Page 110, last paragraph

The text states:

“In general, the cost-effectiveness outcomes reflect the increased effectiveness of dimethyl fumarate in terms of 3 months sustained disease progression up the EDSS scale and of annualised relapse rates when compared to the comparators except for natalizumab; and the high list price for dimethyl fumarate compared to the interferon drugs and glatiramer acetate. Using the list price for dimethyl fumarate, dimethyl fumarate is not cost-effective. When the manufacturer’s proposed PAS price is used for dimethyl fumarate compared to the list prices for other drugs it becomes cost-effective, but this analysis is limited due to the inclusion of the discounted price for only one drug when discounted prices are available to the DoH for all comparators.”

Should read:

“In general, the cost-effectiveness outcomes reflect the increased effectiveness of dimethyl fumarate in terms of 3 months sustained disease progression up the EDSS scale and of annualised relapse rates when compared to the comparators except for natalizumab; and the high list price for dimethyl fumarate compared to the interferon drugs and glatiramer acetate. Using the list price for dimethyl fumarate, dimethyl fumarate is not cost-effective. When the manufacturer’s proposed PAS price is used for dimethyl fumarate compared to the list prices for other drugs it becomes cost-effective, but this analysis is limited due to the inclusion of the discounted price for only one drug when discounted prices are available to the DoH for many of the comparators.”