NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Dimethyl fumarate for treating relapsing-remitting multiple sclerosis

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness evidence

- The trials for dimethyl fumarate lasted 2 years. Treatment is anticipated to be life-long. What is the Committee's view on the uncertainty relating to the long-term treatment effect of dimethyl fumarate?
- The population in the anticipated marketing authorisation for dimethyl fumarate is 'adults with relapsing-remitting multiple sclerosis'. In the DEFINE and CONFIRM trial populations this group had a baseline relapse rate of 1.3 and 1.4 per year respectively (in line with the Association for British Neurologist guidelines for prescribing beta interferons or glatiramer acetate which defines adults with active relapsing disease as having 2 or more clinically significant relapses in the previous 2 years), whereas the UK population has an annualised relapse rate of approximately 0.8 per year as estimated by the ERG. Are the trial populations generalisable?
- The trial protocols defined relapses as new or recurrent neurologic symptoms not associated with fever or infection, lasting more than or equal to 24 hours, and showing new objective neurological findings upon examination. How prone to misclassification is this endpoint?

- Given that the incidence of flushing is considerably higher in patients taking dimethyl fumarate compared with placebo, does the Committee consider this may have led to de facto unblinding?
- The manufacturer did not provide analyses for subgroups defined in the scope including **rapidly evolving severe** relapsing-remitting multiple sclerosis or **highly active** relapsing-remitting multiple sclerosis populations for which NICE recommends fingolimod and natalizumab. Instead, it used the whole population from the trials to compare dimethyl fumarate with fingolimod and natalizumab. What is the view of the Committee on the efficacy of dimethyl fumarate in these subgroups?
- Regarding another subgroup, treatment naive compared with treatment experienced, the manufacturer notes the effect size of the subgroups were comparable with the overall trial population, whereas the ERG noted that there was consistently a larger effect of dimethyl fumarate compared with placebo in treatment naïve patients. However, the ERG acknowledged limitations of subgroup analyses. What is the Committee view on the treatment effect between treatment naïve and treatment experienced patients?
- The ERG considered that measuring sustained disability progression for 6 months is more appropriate than for 3 months, when patients may still recover but that at 6 months there is less clear evidence of benefit with dimethyl fumarate for reducing disability progression. What is the Committee's view on when disability progression should be measured?
- For the mixed treatment comparison, the ERG noted differences in the patient populations between the studies. What is the Committee's view on these differences?

Cost effectiveness evidence

- The choice of comparator is a key driver of cost effectiveness. What does the Committee consider to be the most appropriate comparator(s) for dimethyl fumarate? Should dimethyl fumarate be compared with a blended comparator (that is, a weighted average of the treatments currently used in UK clinical practice)?

- The manufacturer's economic model, similar to models used in previous NICE technology appraisals, allows patients to move to higher or lower EDSS health states. Does the Committee consider that the structure of the model reflects the experience of patients with relapsing-remitting multiple sclerosis? Is the cycle length of 1 year appropriate? Does the distribution of EDSS scores at baseline reflect the distribution in the UK population?
- The ERG commented that probabilistic ICERs are more appropriate than deterministic ICERs because the model is non-linear, but that the manufacturer did not account fully for uncertainty because it did not fit distributions around all parameters. The ERG noted that the manufacturer had not assigned probability distributions to, for example, the parameter accounting for treatment waning over time and the annual risk of stopping treatment. The ERG explained that these 2 parameters have a significant effect on the estimated ICERs because disease progression is the key driver of the economic model. What is the Committees view on this?
- The ERG commented that when patients stop treatment they progress more quickly through the EDSS health states. Because there is a larger reduction in costs than in QALYs, the more patients that stop treatment, the more cost effective the treatment appears. The ERG noted that the ICER of dimethyl fumarate compared with an active treatment would never be smaller than the ICER of dimethyl fumarate compared with best supportive care, which was not a specified comparator in the scope. What is the Committee's view on the exclusion of 'best supportive care' as comparator?
- In clinical practice patients who stop treatment because of adverse reactions will take another active treatment if one with a differing side effect profile is available. Also, patients who progress to secondary progressive multiple sclerosis are likely to take some form of active treatment but this scenario has not be included in the manufacturer's economic model. Would including a scenario allowing people to switch treatments after failure better reflect clinical practice?
- To inform the parameters related to the natural history of multiple sclerosis, the manufacturer used trial data rather than the London Ontario observational

dataset. What do the Committee view as the best available evidence for informing the natural history of relapsing-remitting multiple sclerosis?

- The manufacturer incorporated an effect of waning treatment beyond the 2 years of the trials in its economic model. Does the Committee's believe this adequately addresses uncertainty relating to the long-term treatment effect of dimethyl fumarate?
- To estimate EDSS state costs, 3 publications are available that use the same resource use data but use different unit costs. The ERG considered that the cost of a relapse may be too high in the manufacturer's economic model (£2,208) because only 20% of patients with relapse require hospitalisation. What does the Committee's consider the most reasonable estimates of cost for the EDSS states and per relapse?
- The ERG noted that:
    - utility values from the dimethyl fumarate trials for 'people with relapsing-remitting multiple sclerosis without relapse' may underestimate the health-related quality of life.
    - that the utility values reported in the UK Multiple Sclerosis survey (used to estimate the decrements between: relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis; and between relapsed and non-relapsed patients in the manufacturer's economic model) did not exactly reflect the population defined in the scope (as only 35.5% of patients in the population in the survey have relapsing-remitting multiple sclerosis).

  What does the Committee consider the most reasonable estimates of utility? What is the Committees view on taking into account carer disutility?

1 Background: clinical need and practice

1.1 Multiple sclerosis is a chronic, autoimmune disease of the central nervous system damaging myelin and resulting in inflammation and tissue damage. This impairs transmission of electrical impulses between the brain, spinal cord and other parts of the body, and leads in most patients

to progressive neurological impairment and severe disability. Symptoms can include pain, poor muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, vision problems and cognitive impairment. The causes of multiple sclerosis are unknown, but genetic and environmental factors play a role. Smoking is a risk factor for multiple sclerosis, as is distance from the equator, suggesting a role for ultraviolet radiation or vitamin D.

1.2 Approximately 100,000 people in the UK have multiple sclerosis, and about 2500 people are newly diagnosed each year. Most people with diagnosed with multiple sclerosis are between the ages of 20 and 40 years, and it is approximately three times more common in women than in men. Multiple sclerosis has an unpredictable course with variable severity and speed of progression. ‘Relapsing-remitting’ multiple sclerosis affects approximately 85% of people at time of diagnosis, and is characterised by periods of remission followed by relapses. A subform of relapsing-remitting multiple sclerosis labelled ‘highly active’ characterises more severe disease defined by the number and severity of relapses and by disability caused from the persistent effects of relapse. Highly active relapsing-remitting multiple sclerosis can include:

- ‘Rapidly-evolving’ severe relapsing-remitting multiple sclerosis defined:
    - by 2 or more disabling relapses in 1 year, **and**
        - 1 or more gadolinium-enhancing lesions on brain MRI **or** a significant increase in T2 lesion load compared with a previous MRI.
- Adults with high disease activity despite treatment with a beta interferon (normally at least one year of treatment). Patients should have:

- had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion, **or**
- an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

The progression of the disease is generally monitored by routine clinical assessment (neurologist visits) and several tests that measure full blood count, renal function and liver function.

1.3 Within 15 years of diagnosis of relapsing-remitting multiple sclerosis around 65% of patients will develop a form of disease called 'secondary progressive multiple sclerosis' which is characterised by persisting or increasing disability with or without relapses. Primary progressive multiple sclerosis affects approximately 15% of people at time of diagnosis. It is characterised by gradual disability progression from onset, rather than appearing as relapses.

1.4 The life expectancy of patients with multiple sclerosis is between 5 and 10 years shorter than in the general population and there is no cure. Treatment aims to decrease the frequency and severity of relapses, reduce lesions observed on brain and spinal MRIs, slow physical disability, and maintain or improve patients' quality of life. Current pharmacological management of relapsing-remitting multiple sclerosis includes the first-line use of disease-modifying therapies to reduce the frequency and severity of relapses. These include beta interferon and glatiramer acetate which are not currently recommended by NICE (technology appraisal guidance 32; see Appendix A), but are available in the NHS through a risk-sharing scheme (based on an agreement between the Department of Health and the manufacturers). Beta interferon and glatiramer acetate are prescribed according to the criteria described in the Association for British Neurologist (ABN) Guidelines. This guideline states that patients eligible for treatment are adults who can walk (maximum

Expanded Disability Status Scale (EDSS) score of 6.5 (higher numbers reflect great disability) with active relapsing disease defined as 2 clinically significant relapses in the previous 2 years. The ABN Guidelines also state that "neurologists may, in certain circumstances where the evidence for efficacy is less secure, also consider advising treatment after discussion with the patient concerning the risks and benefits. For example:

- patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes (that is, development of multiple sclerosis).
- patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity (that is, meet the revised McDonald criteria for MS).
- individuals aged less than 18 with relapsing remitting multiple sclerosis."

1.5 In practice, clinicians may offer as second line treatment a different beta interferon or glatiramer acetate, or escalate the dose of the existing beta interferon to people whose disease has responded inadequately to first-line treatment. Some people experience problems with beta interferon and glatiramer acetate because they are self-injected, and/or poorly tolerated (flu-like symptoms, fatigue, depression). For people with rapidly-evolving severe relapsing-remitting multiple sclerosis, natalizumab is recommended as an option (NICE technology appraisal guidance 127; see Appendix A). For adults with highly active relapsing-remitting multiple sclerosis, NICE has recommended fingolimod (with a patient access scheme), as an option for the treatment of who have an unchanged relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon (NICE technology appraisal guidance 254; see Appendix A). There is no set treatment pathway for

multiple sclerosis, and treatment choices are based on considerations of efficacy and safety, as well as on patient preference.

1.6 The Multiple Sclerosis Society published the findings of a survey in April 2013 showing major disparities across the UK in access to treatments, in particular, that 60% of people with relapsing forms of multiple sclerosis are not taking a disease-modifying therapy. (see http://www.mssociety.org.uk/ms-news/2013/04/ms-care-lottery-revealed-groundbreaking-ms-society-research). The Multiple Sclerosis Society stated it used a "very basic and broad interpretation of eligibility and that would be people with relapsing forms of multiple sclerosis".

2 The technology

2.1 Dimethyl fumarate (Tecfidera, Biogen Idec) derives from fumaric acid, promotes anti-inflammatory activity, and can inhibit expression of pro-inflammatory cytokines and adhesion molecules. Dimethyl fumarate has an anticipated UK marketing authorisation for the treatment of 'adult patients with relapsing-remitting multiple sclerosis'.

2.2 The draft summary of product characteristics lists the following adverse reactions for dimethyl fumarate: gastroenteritis, lymphopenia, leucopenia, hypersensitivity, burning sensation, flushing, hot flush, diarrhoea, nausea, abdominal pain upper, abdominal pain, vomiting, dyspepsia, gastritis, gastrointestinal disorder, pruritus, rash, erythema, proteinuria, feeling hot, ketones measured in urine, albumin urine present, aspartate aminotransferase increased, alanine aminotransferase increased and white blood cell count decreased. For full details of adverse reactions and contraindications, see the draft summary of product characteristics.

2.3 Dimethyl fumarate is administered orally. In the first week of treatment the recommended dosage is 120 mg twice daily, thereafter the recommended dosage is 240 mg twice daily and treatment continues as long as patients benefit clinically, or until they experience unacceptable adverse reactions. The frequency of flushing and gastrointestinal adverse reactions may be

managed by temporarily (up to a month) reducing the dosage to 120 mg twice daily. The price for a pack of 120 mg tablets (14 tablets per pack) and 240 mg tablets (56 tablets per pack) is £343 and £1373 respectively (excluding VAT; manufacturer's submission). Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of dimethyl fumarate has agreed a patient access scheme with the Department of Health, with a simple discount applied at the point of purchase or invoice. The level of discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of dimethyl fumarate within its licensed indication for the treatment of relapsing-remitting multiple sclerosis.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with relapsing-remitting multiple sclerosis	Adult patients (≥ 18 years old) with relapsing-remitting multiple sclerosis

The population addressed in the submission was updated by the manufacturer to reflect the anticipated UK marketing authorisation.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	Dimethyl fumarate	
Comparators	• Beta-interferon • Glatiramer acetate • Natalizumab (for patients with rapidly-evolving severe relapsing-remitting multiple sclerosis) • Fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon)	

The ERG commented that the manufacturer included only 1 form of beta interferon 1-b (that is, Betaferon). The ERG noted that the form of beta interferon 1-b (Extavia) excluded from the manufacturer's submission is not covered by the NHS Risk

Sharing Scheme. However, the Department of Health has advised that clinicians should be free to choose Betaferon or Extavia.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	• Relapse rate • Severity of relapse • Disability (for example, expanded disability status scale [EDSS]) • Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • Freedom of disease activity • Mortality • Adverse effects of treatment • Health-related quality of life	• MRI parameters • Relapse rate • Disability (for example, expanded disability status scale [EDSS]) • Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • Freedom of disease activity • Mortality • Adverse effects of treatment • Health-related quality of life

The manufacturer included results from MRI scanning as an outcome in its submission. It noted results from MRI may reflect disease activity in the absence of relapses or disability progression. The manufacturer's phase III trials did not include the outcome severity of relapse so it did not include this outcome in its submission.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. This includes the arrangements within the risk-sharing scheme, which was agreed for the supply of disease modifying treatments for Multiple Sclerosis in the NHS (see Health Service Circular 2002/004).	

	Final scope issued by NICE	Decision problem addressed in the submission
Subgroups to be considered	If the evidence allows, the following subgroups of patients will be considered: • patients with relapsing-remitting multiple sclerosis whose disease has inadequately responded to treatment with disease modifying therapy • patients with relapsing-remitting multiple sclerosis whose disease is intolerant to treatment with disease modifying therapy • patients with highly active relapsing-remitting multiple sclerosis • patients with rapidly evolving severe relapsing-remitting multiple sclerosis	No subgroups considered

The manufacturer did not include any analysis of the subgroups listed in the final scope, noting that:

- dimethyl fumarate is indicated for all adult patients with relapsing-remitting multiple sclerosis
- these subgroups have not been specifically examined in the majority of trials and therefore there is a lack of data for the comparators
- these subgroups comprise the overall populations in these trials and are therefore indicative of efficacy in these subgroups

The manufacturer stated that the eligible population for dimethyl fumarate is:

- treatment naïve patients (including newly diagnosed and those who have not received a disease modifying therapy);
- those who have discontinued a previous treatment due to lack of efficacy or tolerability; and

- patients who are sub-optimally treated or dissatisfied with their current treatment.

The ERG commented that a substantial proportion of patients who would be eligible for dimethyl fumarate under the current therapeutic indication recommended by the Committee for Medicinal Products for Human Use (CHMP) currently receive no disease modifying therapy. It considered that these patients may be receiving best supportive care, which is not included as a comparator in the NICE scope or in the manufacturer's submission.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of dimethyl fumarate for treating adults with relapsing-remitting multiple sclerosis. It identified 2 phase III randomised controlled trials (RCTs): DEFINE and CONFIRM.

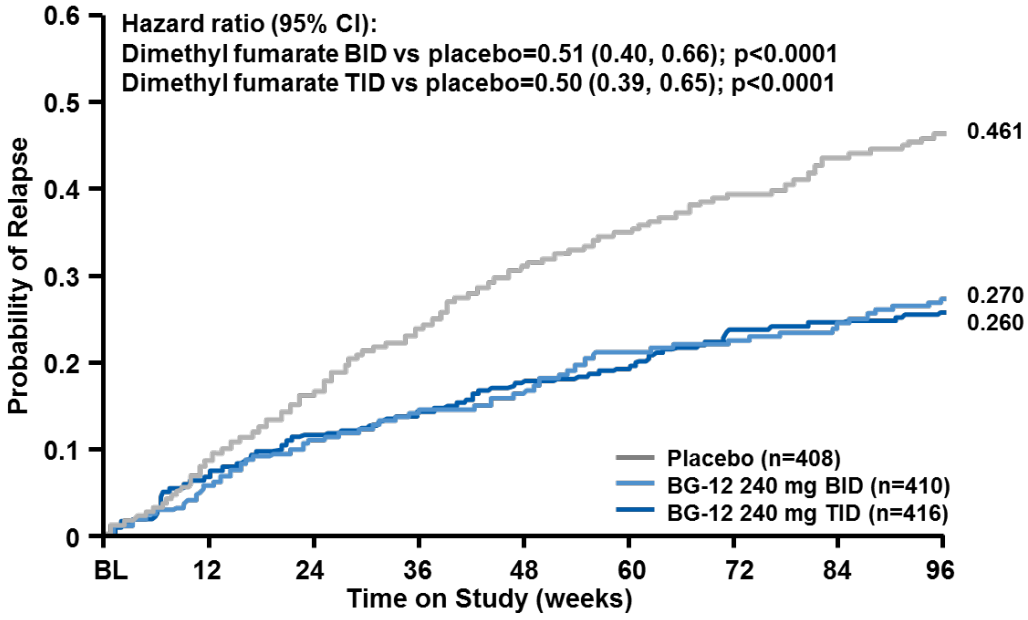
4.2 The DEFINE trial was an international multicentre (198 centres in 28 countries) double-blind phase III RCT in 1237 adults with relapsing-remitting multiple sclerosis. Patients were stratified by centre and randomised in a 1:1:1 ratio to dimethyl fumarate 240 mg twice daily (n=410), dimethyl fumarate 240 mg thrice daily (n=416) or placebo (n=408). The CONFIRM trial was an international multicentre (200 centres in 28 countries) double-blind phase III RCT in 1430 adults with relapsing-remitting multiple sclerosis. Patients were stratified by centre and randomised in a 1:1:1:1 ratio to dimethyl fumarate 240 mg twice daily (n=359), dimethyl fumarate 240 mg thrice daily (n=345), glatiramer acetate 20 mg once daily (n=350; open-label) or placebo (n=363). In both the DEFINE and CONFIRM trials, patients were treated for 96 weeks and had a follow-up visit at 100 weeks if they completed treatment. Patients stopped treatment if they did not tolerate study drug or they withdrew consent. Only data relating to the licensed dosage of dimethyl fumarate (240 mg twice daily) were presented in the manufacturer's submission.

4.3 Patients were eligible for inclusion in the DEFINE and CONFIRM trials if they were aged between 18 and 55 years, had a diagnosis of relapsing-remitting multiple sclerosis confirmed by the McDonald criteria, an Expanded Disability Status Scale (EDSS) score of between 0 and 5 (the EDSS ranges from 0 to 10 with 0.5-unit increments representing higher levels of disability) and had either at least 1 relapse during the previous year and a previous MRI scan showing lesions consistent with multiple sclerosis, or gadolinium-enhancing lesions on MRI scans done within 6 weeks of randomisation. The manufacturer noted there were no significant differences in baseline characteristics between the treatment groups of the DEFINE and CONFIRM trials. Most patients in the DEFINE and CONFIRM trials were white (DEFINE=79%, CONFIRM=84%) and female (DEFINE=74%, CONFIRM=70%). The mean age of patients were 38.5 years old and 37.3 years old in the DEFINE and CONFIRM trials respectively. Patients were enrolled across Central and North America, Asia, Eastern and Western Europe, the Middle East and Australasia. In the DEFINE trial, 29 patients were treated at 7 UK centres. The CONFIRM trial did not include any UK centres.

4.4 The primary outcome measure in the DEFINE and CONFIRM trials was the proportion of patients with a relapse at 2 years and the annualised relapse rate at 2 years respectively. Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting more than or equal to 24 hours, and with new objective neurological findings. An intention-to-treat population was the primary population for the analysis of efficacy outcomes in both trials. In the DEFINE trial, the proportion of patients with a relapse at 2 years was 27% with dimethyl fumarate and 46% with placebo (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.40 to 0.66), see the Kaplan-Meier estimate (Figure 1). In the CONFIRM trial, the adjusted annualised relapse rate at 2 years was 0.22 with dimethyl fumarate and 0.40 with placebo (relative risk [RR] 0.56, 95% CI 0.42 to 0.74), and 0.29 with glatiramer acetate (RR compared with dimethyl fumarate not reported). The CONFIRM trial was

not powered to detect differences between dimethyl fumarate and glatiramer acetate (active comparator). The manufacturer performed a number of sensitivity analyses that supported the results of the primary efficacy analysis of the DEFINE and CONFIRM trials comparing dimethyl fumarate with placebo, for further details see pages 71–74 of the manufacturer's submission.

Figure 1: Kaplan-Meier estimate of the proportion of patients relapsed at 2 years (DEFINE) [page 71, figure 5, manufacturer's submission]



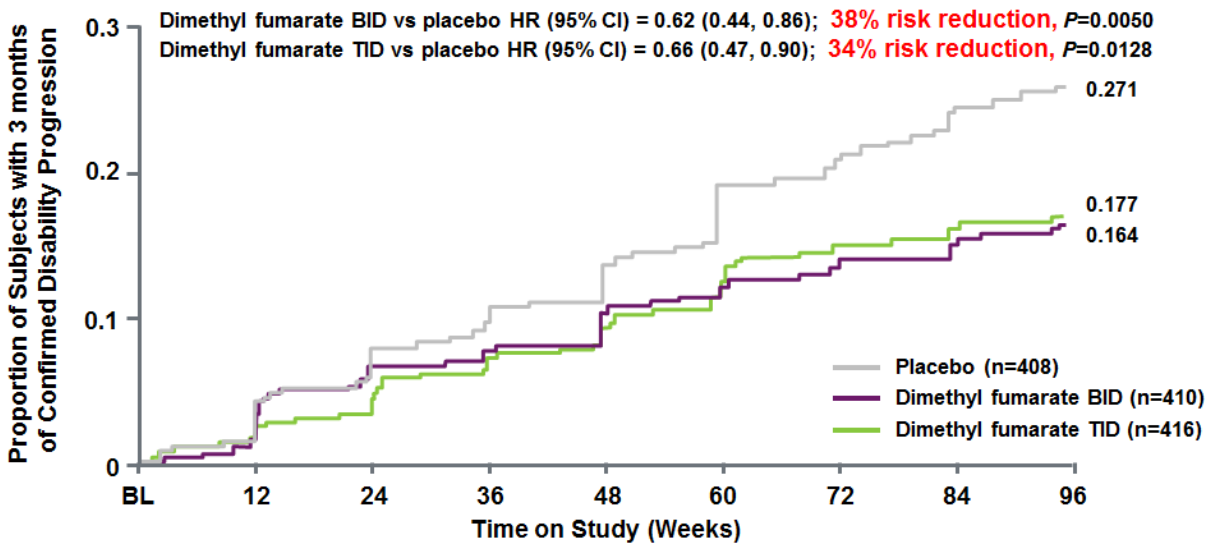
Number of patients at risk

Placebo	408	356	321	282	243	224	205	190	115
240 mg BID	410	353	324	303	286	267	255	243	154
240 mg TID	416	346	322	301	286	270	251	244	166

4.5 Secondary outcomes reported in the DEFINE trial included annualised relapse rate at 2 years, in the CONFIRM trial the proportion of patients with a relapse at 2 years, and in the DEFINE and CONFIRM trials, progression of disability on the EDSS and MRI lesion number (in a subset of patients) at 2 years. In the DEFINE trial, the annualised relapse rate at 2 years was 0.17 with dimethyl fumarate and 0.36 with placebo (RR 0.47, 95% CI 0.37 to 0.61). In the CONFIRM trial, the proportion of patients with a relapse at 2 years was 29% with dimethyl fumarate and 41% with placebo (HR 0.66, 95% CI 0.51 to 0.86). Patients taking dimethyl fumarate

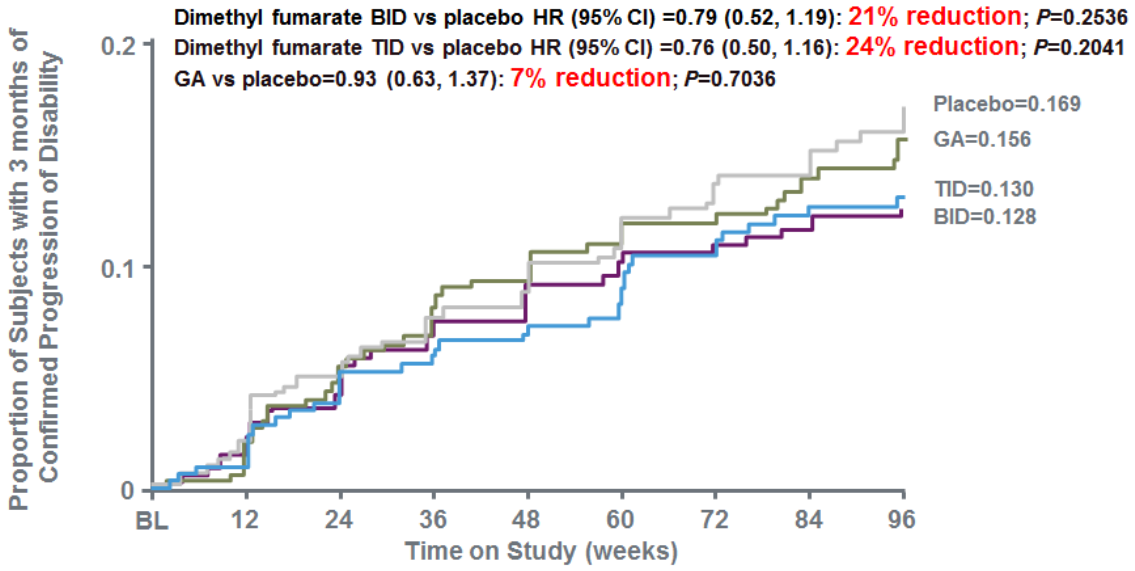
had a reduced risk of disability progression sustained for 3 months at 2 years compared with placebo in the DEFINE (see Figure 2; 16% compared with 27%; HR 0.62, 95% CI 0.44 to 0.87) and CONFIRM trials (see Figure 3; 13% compared with 17%; HR 0.79, 95% CI 0.52 to 1.19). The manufacturer suggested that the results of 3 month disability progression in the CONFIRM trial may have been affected by a higher proportion of patients in the placebo arm who may or may not have progressed being censored compared with dimethyl fumarate. It explained that patients were censored if they withdrew from the study or switched treatments before 3 month progression could be confirmed. A pre-planned sensitivity analysis of disability progression sustained for 6 months at 2 years comparing dimethyl fumarate with placebo in the DEFINE (HR 0.77, 95% CI 0.52 to 1.14) and CONFIRM trials (HR 0.62, % CI 0.37 to 1.03) was presented in the draft Committee for Medicinal Products for Human Use (CHMP) assessment report. The number of lesions were significantly reduced on T1-, T2-weighted and gadolinium-enhancing MRI at 2 years with dimethyl fumarate compared with placebo in the DEFINE and CONFIRM trials respectively, for further details see pages 76–78 of the manufacturer's submission. The manufacturer also presented a post hoc analysis of freedom from disease activity (see Figure 4), for further details see pages 100–101 of the manufacturer's submission. For a summary of the results for the primary and secondary outcomes for DEFINE and CONFIRM trials see Table 1.

Figure 2: Time to 3-month confirmed disability progression (DEFINE) [page 71, figure 9, manufacturer's submission]



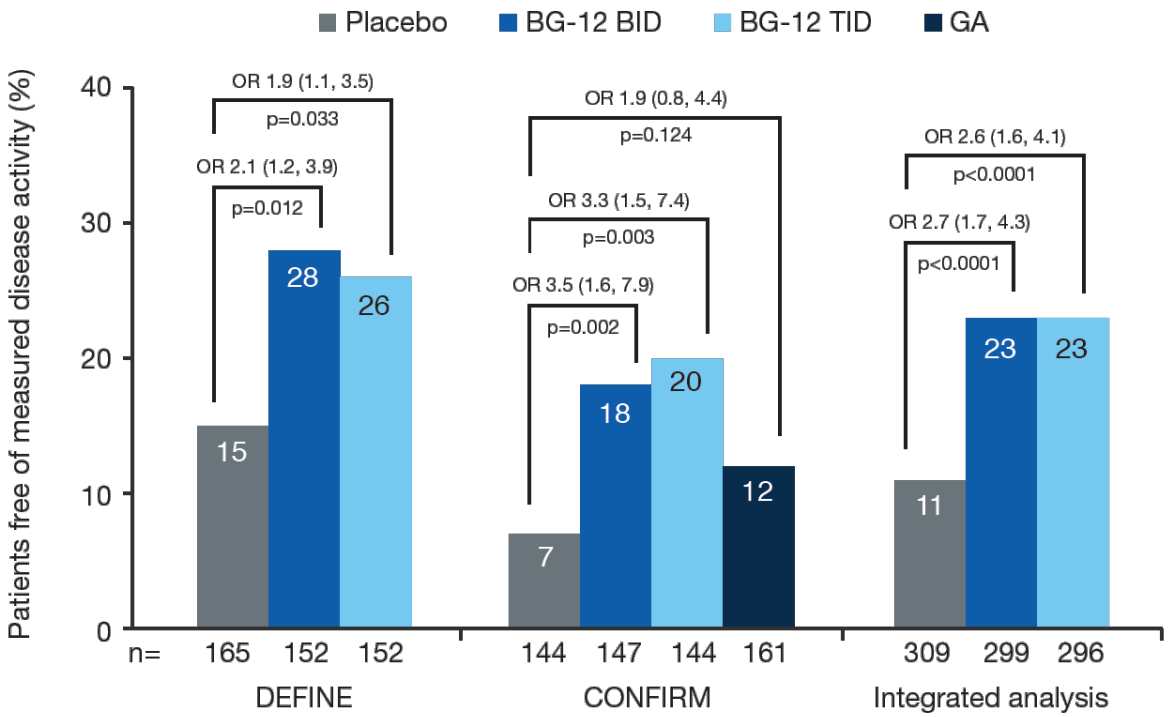
Abbreviations: BID, twice daily; HR, hazard ratio; TID, three times daily.

Figure 3: Time to 3-month confirmed disability progression (CONFIRM) [page 76, figure 10, manufacturer's submission]



Abbreviations: BID, twice daily; GA, glatiramer acetate; HR, hazard ratio; TID, three times daily.

Figure 4: Freedom from combined clinical and radiological disease activity in DEFINE and CONFIRM [page 101, figure 11, manufacturer's submission]*



Abbreviations: BID, twice daily; GA, glatiramer acetate; OR, odds ratio; TID, three times daily. *Integrated analysis: pooled analysis of the DEFINE and CONFIRM trials.

Table 1: Summary of the results of the primary and secondary outcomes of the DEFINE and CONFIRM trials

Clinical outcomes		DEFINE		CONFIRM		
		Dimethyl fumarate	Placebo	Dimethyl fumarate	GA	Placebo
Proportion of patients relapsing at 2 years	Estimated proportion of patients	0.27	0.46	0.291	0.321	0.410
	Hazard ratio† (95% CI)	0.51 (0.40, 0.66)	-	0.66 (0.51, 0.86)	0.71 (0.55, 0.92)	-
	p value†	<0.0001	-	0.0020	0.0097	-
	% reduction *vs* placebo	49%	-	34%	29%	-
Annualised relapse rate at 2 years	ARR: relative risk (95% CI)	0.17 (0.14, 0.21)	0.36 (0.30, 0.44)	0.22 (0.18, 0.28)	0.29 (0.23, 0.35)	0.40 (0.33, 0.49)
	Rate ratio‡ (95% CI)	0.47 (0.37, 0.61)	-	0.56 (0.42, 0.74)	0.71 (0.55, 0.93)	-
	p value†	<0.0001	-	<0.0001	0.0128	-
	% reduction *vs* placebo	53%	-	44%	29%	-
EDSS disability progression sustained for 3 months at 2 years	Proportion progressed at 2 years (%)	16	27	13	16	17
	Hazard ratio† (95% CI)	0.62 (0.44, 0.87)	-	0.79 (0.52, 1.19)	0.93 (0.63, 1.37)	-
	p value†	0.0050	-	0.2536	0.7036	-
	% reduction *vs* placebo	38%	-	21%	7%	
No. T2 lesions	Mean number (95% CI)	2.6 (2.0, 3.5)	17.0 (12.9, 22.4)	5.1 (3.9, 6.6)	8.0 (6.3, 10.2)	17.0 (13.5, 22.4)
	Mean ratio† (95% CI)	0.15 (0.10, 0.23)	-	0.29 (0.21, 0.41)	0.46 (0.33, 0.63)	-
	p value†	<0.0001	-	<0.0001	<0.0001	-
	% reduction *vs* placebo	85%	-	71%	54%	-
No. T1 lesions	Mean number±SD	2.0±4.1	5.7±8.3	3.0 (2.3, 4.0)	4.1 (3.2, 5.3)	7.0 (5.3, 9.2)
	Mean ratio† (95% CI)	0.28 (0.20, 0.39)	-	0.43 (0.30, 0.61)	0.59 (0.42, 0.82)	-
	p value†	<0.0001	-	<0.0001	0.0021	-
	% reduction *vs* placebo	NR	NR	57%	41%	-
No. Gd+ lesions	Mean number±SD	0.1±0.6	1.8±4.2	0.5±1.67	0.7±1.75	2.0±5.59
	Odds ratio† (95% CI)	0.10 (0.05, 0.22)	-	0.26 (0.15, 0.46)	0.39 (0.24, 0.65)	-
	p value†	<0.0001	-	<0.0001	0.0003	-
	% reduction *vs* placebo	90%	-	NR	NR	NR

All outcomes are at 2 years. †Versus placebo. Abbreviations: CI, confidence interval; GA, glatiramer acetate; SD, standard deviation.

[redacted]

4.6 The manufacturer presented results for the pre-specified subgroup analyses for the DEFINE and CONFIRM trials in its submission. It stated the results of these analyses were generally consistent with the results for the overall population. The results of the DEFINE trial were similar for treatment naïve (proportion relapsed: HR 0.37, 95% CI 0.24 to 0.57; annualised relapse rate: RR 0.33, 95% CI 0.21 to 0.52; EDSS progression: HR 0.38, 95% CI 0.22 to 0.65) and treatment experienced patients (proportion relapsed: HR 0.65, 95% CI 0.48 to 0.89; annualised relapse rate: RR 0.61, 95% CI 0.45 to 0.84; 3 month disability progression: HR 0.83, 95% CI 0.54 to 1.29), although disability progression was not statistically significantly reduced with dimethyl fumarate compared with placebo for the treatment experienced subgroup. The manufacturer also noted that the results of the CONFIRM trial were similar for treatment naïve (proportion relapsed: HR 0.73, 95% CI 0.51 to 1.05; annualised relapse rate: RR 0.64, 95% CI 0.44 to 0.95; EDSS progression: HR 0.56, 95% CI 0.30 to 1.03) and treatment experienced patients (proportion relapsed: HR 0.57, 95% CI 0.38 to 0.84; annualised relapse rate: RR 0.47, 95% CI 0.31 to 0.69; 3 month disability progression: HR 1.07, 95% CI 0.60 to 1.89). No tests of interaction were presented by the manufacturer. For further details regarding the manufacturer's pre-specified subgroup analyses, see pages 88–99 of the manufacturer's submission.

4.7 The manufacturer presented the results of both a fixed-effects and random-effects meta-analysis of the efficacy and safety outcomes of the DEFINE and CONFIRM trials. It estimated that dimethyl fumarate was significantly better compared with placebo for all efficacy outcomes analysed including disability progression sustained for 3 months at 2 years and 6 months at 2 years. The manufacturer's meta-analysis also estimated that patients taking dimethyl fumarate experienced significantly more gastrointestinal events, flushing and skin reactions compared with placebo or glatiramer acetate. It estimated no difference in the number of

withdrawals for any reason between treatments but significantly more patients taking dimethyl fumarate withdrew because of adverse reactions compared with placebo or glatiramer acetate. For further details regarding the manufacturer's meta-analysis, see pages 101–113 of the manufacturer's submission.

4.8 Both trials measured health-related quality of life using the global wellbeing Visual Analogue Scale (VAS), the Short Form 36 Health Survey (SF-36) and the EuroQol-5 dimensions survey (including the EQ-5D descriptive system and the EQ VAS). In the DEFINE trial, patients randomised to dimethyl fumarate had a significantly higher health-related quality of life compared with placebo when measured by: the mean change in global well-being VAS from baseline (0.4 compared with -4.0; p=0.003), the mean change in the physical component score of the SF-36 from baseline (0.5 compared with -1.4; p=0.000), the mean change in 6 of 8 SF-36 subscales from baseline and mean change in EQ VAS from baseline (-0.3 compared with -4.2; p=0.000). In the CONFIRM trial, patients receiving dimethyl fumarate showed a significantly higher health-related quality of life compared with placebo when measured by: the mean change in global well-being VAS from baseline (0.3 compared with -3.9; p=0.000), the mean change in the physical component score of the SF-36 from baseline (0.5 compared with -0.7; p=0.022) and the mean change in 3 of 8 SF-36 subscales from baseline.

4.9 The manufacturer reported that the overall incidence of adverse reactions were similar between patients taking dimethyl fumarate and placebo respectively (96% compared with 95% in DEFINE, and 94% compared with 92% in CONFIRM). The most common adverse reactions reported for dimethyl fumarate compared with placebo were flushing (38% compared with 5% in DEFINE and 31% compared with 4% in CONFIRM), hot flush (8% compared with 2% and 5% compared with 2% in CONFIRM), abdominal pain upper (10% compared with 7% and 10% compared with 5% in CONFIRM), nausea (13% compared with 9% and 11% compared

with 8% in CONFIRM) and vomiting (10% compared with 6% and 7% compared with 4% in CONFIRM). The manufacturer noted that most adverse reactions were mild to moderate in severity and that incidences were highest in the first month and decreased thereafter. Sixteen percent of patients taking dimethyl fumarate and 13% of patients taking placebo stopped treatment because of adverse reactions in the DEFINE trial, and 12% of patients taking dimethyl fumarate compared with 10% of patients taking placebo stopped treatment because of adverse reactions in the CONFIRM trial. The manufacturer reported that the incidence of serious adverse reactions was low in patients taking dimethyl fumarate and comparable with patients taking placebo (18% compared with 21% in DEFINE and 17% compared with 22% in CONFIRM).

4.10 The manufacturer conducted a mixed treatment comparison using a fixed-effects frequentist approach of 27 trials that assessed the relative effectiveness of outcomes including annualised relapse rate, proportion of relapsing patients at 24 months, change in EDSS score from baseline and confirmed disability progression sustained for 3 months at 2 years. The following comparators were included in the manufacturer's mixed treatment comparison: beta interferon-1a (Avonex, Rebif-22, Rebif-44), beta interferon-1b (Betaferon), glatiramer acetate, fingolimod, natalizumab and placebo.

4.11 The manufacturer presented results of the mixed treatment comparison unadjusted for covariates. The manufacturer undertook a covariate analysis that showed they had little or no impact on the outcomes of interest. The manufacturer's mixed treatment comparison suggested dimethyl fumarate reduces annualised relapse rate and the proportion of patients with relapses at 2 years compared with placebo, glatiramer acetate and all beta interferons (see Figures 5 and 6). The manufacturer's mixed treatment comparison also suggested dimethyl fumarate reduces disability progression sustained for 3 months at 2 years compared with placebo (see Figure 7). No differences were estimated between dimethyl

fumarate and any comparator, including placebo, for disability progression sustained for 6 months at 2 years (see Figure 8). The manufacturer labelled the effect size and credible intervals from its mixed treatment comparison as academic in confidence; for further details see pages 139–152 of the manufacturer's submission. The manufacturer stated that it had not explored the subgroups specified in the scope of the appraisal because they had not been analysed in most of the trials included in its mixed treatment comparison.

Figure 5: Results of manufacturers mixed treatment comparison for annualised relapse rate [page 139, figure 21, manufacturer's submission]

[redacted] ARR <1 indicates better efficacy of intervention.
Abbreviations: ARR, annualised relapse rate; BG00012, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; tid, three times daily; tiw, three times weekly.

Figure 6: Results of the manufacturer's mixed treatment comparison for proportion of patients with relapses at 2 years [page 140-41, figure 24, manufacturer's submission]

[redacted] RR <1 indicates better efficacy of intervention.

Figure 7: Results of the manufacturer's mixed treatment comparison for confirmed disability progression sustained for 3 months at 2 years [page 10, figure 1, manufacturer's response to clarification]*

[redacted] HR <1 indicates better efficacy of intervention;
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; HR, Hazard Ratio; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; tid, three times daily; tiw, three times weekly.*** *Modelled as hazard ratios during clarification (preferred by ERG)***

Figure 8: Results of the manufacturer's mixed treatment comparison for confirmed disability progression sustained for 6 months at 2 years [page 10, figure 2, manufacturer's response to clarification]

[redacted] HR <1 indicates better efficacy of intervention; **** Modelled as hazard ratios during clarification (as preferred by ERG)***

[redacted]

ERG comments on the clinical effectiveness data

4.12 The ERG stated that the DEFINE and CONFIRM trials were of good quality and had a low risk of bias. The ERG commented that the trial populations more closely reflects people with relapsing-remitting multiple sclerosis who meet the Association of British Neurologist (ABN) prescribing criteria for disease-modifying therapy (that is, adults with active relapsing disease defined as 2 or more clinically significant relapses in the previous 2 years) than people with relapsing-remitting multiple sclerosis in general. The ERG explained:

- Patients in the NHS Risk Sharing Scheme (patients taking beta interferon or glatiramer acetate who need to meet the ABN prescribing criteria to be eligible for treatment) have a mean of 2.9 relapses in the last 2 years whereas the ERG's clinical advisors suggested that the annualised relapse rate in people with relapsing-remitting multiple sclerosis generally approximates 0.8.
- The baseline annualised relapse rates in the DEFINE and CONFIRM trials were 1.3 and 1.4 respectively (which reflected the inclusion criteria that patients were required to have 1 or more relapse in the year before randomisation).

Therefore, the ERG considered that the effectiveness of dimethyl fumarate for the (whole of) prevalent relapsing-remitting multiple sclerosis population is uncertain. It also noted that the mean EDSS scores were slightly lower in the trial populations compared with the NHS Risk Sharing Scheme population. The ERG commented that the trial populations were broadly representative of people with relapsing-remitting multiple sclerosis seen in UK clinical practice in terms of age, sex and disease duration. The ERG noted however that the proportion of patients previously treated with a disease modifying therapy in the DEFINE trial (41%) may be higher than observed in UK clinical population based on the findings of a longitudinal study of multiple sclerosis in 1 English region (31%). Most patients

previously treated in the trials had only taken 1 disease modifying therapy and this may not be representative of the current UK population. However, overall, the ERG did not consider the differences between the trial populations and the UK clinical population to be clinically significant.

4.13 The ERG stated that 3 month disability progression has been used as an outcome measure in previous NICE technology appraisals of multiple sclerosis ('Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis' [NICE technology appraisal guidance 254]). However, it is not consistent with the EMA draft guideline that advises the use of 6 month disability progression (because at 3 months the possibility of recovery exists). Because, the manufacturer's data for 6 month sustained disability progression showed less clear evidence of benefit than the 3 month sustained disability progression, the ERG concluded some uncertainty remained regarding the effect of dimethyl fumarate on disability progression.

4.14 The ERG commented that there is potentially a difference in the effect sizes in some of the subgroups in the DEFINE trial despite the manufacturer suggesting the clinical effectiveness of the subgroups were generally comparable with the overall trial population. It noted there was consistently a larger effect of dimethyl fumarate compared with placebo in treatment naïve patients than in treatment experienced patients but the confidence intervals of the 2 groups overlapped, and that the subgroup analyses suggested a larger benefit in patients with a baseline EDSS score of less than or equal to 2 compared with a baseline EDSS score of more than or equal to 2. The ERG acknowledged that the subgroup analyses of the CONFIRM trial did generally show a consistency of effect between patient subgroups. However, it concluded that because of the inherent limitations of analyses of subgroups, it is not appropriate to draw strong conclusions based on these data.

[redacted]

4.15 The ERG stated that the rate of adverse reactions and serious adverse reactions for patients taking dimethyl fumarate were comparable to placebo. The ERG noted that higher incidences of flushing and gastrointestinal events were reported but appeared to be confined to the first months of treatment, although it was unclear whether this was also the case for skin reactions. The ERG was aware of progressive multifocal leukoencephalopathy occurring in 3 patients taking Fumaderm and 1 patient taking a compounded formulation of dimethyl fumarate and copper monomethyl fumarate. The ERG stated if progressive multifocal leukoencephalopathy were considered to be an adverse reaction of dimethyl fumarate, guidance for when to stop treatment would be needed in clinical practice.

4.16 The ERG stated that the 2 year duration of trials was short compared with:

- The duration of the disease.
- The length of time people with relapsing-remitting multiple sclerosis would be expected to take disease modifying therapy.

It therefore concluded that there is considerable uncertainty relating to the long term efficacy and safety of dimethyl fumarate.

[redacted]

4.17 The ERG commented that the manufacturer's mixed treatment includes all relevant trials. It noted that these trials appear to be at low, or unclear, risk of bias although the manufacturer did not assess allocation concealment. The ERG stated that some networks were sparsely populated because of the number of outcomes analysed and the availability of data from the

included trials. It also noted a moderate level of clinical and methodological heterogeneity between the trials included. This included differences in baseline characteristics such as mean EDSS score and the inclusion criteria regarding the number of relapses in the period before randomisation. For example, the mean or median relapse rate in the year before randomisation ranged between 1.0 and 2.4, which the ERG considered to be clinically important. However, the ERG concluded the level of heterogeneity between trials was not sufficient to make the comparisons unreasonable.

4.18 The ERG stated that using a fixed-effects frequentist approach in the manufacturer's mixed treatment comparison was likely to be appropriate for assessing most of the outcomes because the small number of trials comprising the networks did not allow an estimation of the between-study variance. However, a random-effects model may have been appropriate for assessing the annualised relapse rate. The ERG noted that the estimated confidence intervals for the annualised relapse rate outcome may therefore be slightly underestimated (that is, too narrow).

4.19 The ERG commented that the manufacturer did not address the relative effectiveness of dimethyl fumarate compared with fingolimod or natalizumab in the subgroups specified in the final scope. It acknowledged that the populations included in the trials were broader than defined in their marketing authorisations. However, the ERG concluded that because the manufacturer did not analyse patients with highly active relapsing-remitting multiple sclerosis or patients with rapidly evolving severe relapsing-remitting multiple sclerosis, the relative effectiveness of dimethyl fumarate compared with fingolimod and natalizumab was uncertain in these subgroups respectively.

5 Comments from other consultees

5.1 The professionals groups noted that access to disease-modifying therapies is guided by Association of British Neurologist guidelines and

NICE Technology Appraisals. Despite the availability of national guidelines, the professionals groups commented that geographical variation exists because treatment was commissioned locally until April 2013. It was also noted that there may be differences in how different healthcare professionals interpret the guidelines, for example, when to start treatment. Professional groups differed with regard to the anticipated position in the treatment pathway for dimethyl fumarate. One professional group noted that dimethyl fumarate would be considered for treatment naïve patients, that is, first-line. In contrast, another professional group anticipated that dimethyl fumarate would be positioned after beta-interferon and glatiramer acetate; dimethyl fumarate would therefore be a useful treatment option for those patients who are ineligible for fingolimod.

5.2 The patient group stated that multiple sclerosis is commonly diagnosed at a time when people are developing careers, starting families and taking on financial obligations. The patient group commented that relapses have significant impact on the ability to work leading to the potential loss of earnings for patients and informal carers. The disease affects daily activities and social relationships, and presents emotional challenges for the individual and their family. Recovery from relapses is rare, and disability accumulates with each successive relapse. The patient group noted that the quality and access to care is highly variable throughout the country. New treatments that either reduce the frequency and severity of relapses would be a major benefit for people.

5.3 Patient and professional groups made reference to the results of the DEFINE and CONFIRM trials when discussing the advantages of dimethyl fumarate. The professional group acknowledged that the evidence showing that dimethyl fumarate reduces disability progression was less clear than the evidence showing reduced relapses. However, it concluded that on the whole there is evidence of greater efficacy compared with beta-interferons and glatiramer acetate. The professional group were of the view that the population enrolled in the DEFINE and CONFIRM trials

were reflective of those treated in UK clinical practice. One further advantage acknowledged by the professional and patients groups was that dimethyl fumarate is an oral treatment which patients may prefer to self-injected therapies.

5.4 The patient and professional groups recognised that dimethyl fumarate appears to be well tolerated but patients would need monitoring of blood count, liver function, renal function and cholesterol. It was suggested that administering dimethyl fumarate twice daily may reduce adherence and therefore there is some uncertainty whether the outcomes achieved in the clinical trials can be replicated in clinical practice.

5.5 The patient and professional groups identified a number of issues with regard to implementation. Dimethyl fumarate would not require people to learn how to inject. The groups did not anticipate that the monitoring requirements, staff or facilities would increase compared with currently available treatments. However, it is expected that prescribing dimethyl fumarate will be restricted to specialists and therefore the training of staff will still be needed.

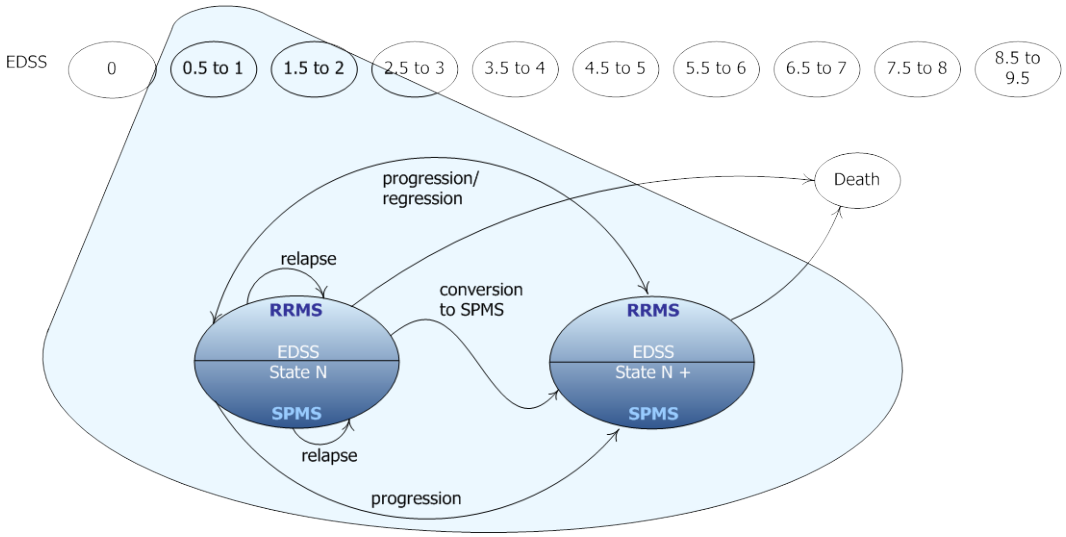
6 Cost-effectiveness evidence

6.1 The manufacturer did not identify any published studies of cost effectiveness of dimethyl fumarate for treating adults with relapsing-remitting multiple sclerosis. It submitted a cohort-based Markov model that reflected the natural history of relapsing-remitting multiple sclerosis with a cycle length of 1 year and assumed a patient can be offered 1 of 8 treatments: dimethyl fumarate, 1 of 3 beta interferon-1a (Avonex, Rebif-22, Rebif-44), beta interferon-1b (Betaferon), glatiramer acetate, fingolimod and natalizumab. The manufacturer conducted the economic analysis from an NHS and Personal Social Services perspective and chose a lifetime horizon of 30 years. Costs and health effects were discounted at an annual rate of 3.5% and a half-cycle correction was applied.

[redacted]

6.2 The manufacturer's model was structurally similar to models used in previous NICE technology appraisal guidance on treatments for multiple sclerosis ('Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis' [NICE technology appraisal guidance 254], 'Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis' [NICE technology appraisal guidance 127] and 'Beta interferon and glatiramer acetate for the treatment of multiple sclerosis' [NICE technology appraisal guidance 32]). The model estimates disease progression through 21 disability states that are defined by EDSS scores (ranging from 0 to 9.5) and account for disability in patients with relapsing–remitting multiple sclerosis (10 states), patients with secondary progressive multiple sclerosis (10 states) and death (see Figure 9). In each cycle of the model, a patient with relapsing–remitting multiple sclerosis can move to a higher or lower EDSS state or remain in the same state. Patients can also advance from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis; however, once a patient reaches this point in the disease course they cannot convert back to relapsing–remitting disease. Only adults with relapsing–remitting multiple sclerosis and an EDSS score of 6 or less are assumed to receive disease-modifying treatment in the model.

Figure 9: Schematic of manufacturer's economic model [page 171, figure 33, manufacturer's submission]



Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis. State N is a patient's EDSS state.

6.3 Patient baseline characteristics were pooled from the DEFINE and CONFIRM trials. The probability of changing EDSS health state or experiencing a relapse was fixed for each EDSS range based on natural history data (underlying disease progression) and trial data (disease progression with treatment). The manufacturer estimated the natural history of disability progression using the placebo arms of the DEFINE and CONFIRM trials up to an EDSS score of 7, and using a longitudinal data set of patients with multiple sclerosis in Ontario, Canada for EDSS scores of more than 7, because of the small number of observations for the more severe EDSS states in the trials. The Ontario longitudinal data set was also used by the manufacturer to estimate the natural history of: i) progressing from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis (by EDSS score) and ii) progressing within the secondary progressive multiple sclerosis health states. The pooled baseline trial data gave the natural history of relapses by EDSS score in patients with an EDSS score of up to 5. The natural history of relapses by EDSS score in patients with an EDSS score of more than 5 were estimated by the manufacturer using data in the literature because the

sample sizes of patients with an EDSS score of more than 5 from trial were too small.

6.4 To estimate clinical effectiveness of each treatment compared with placebo for disability progression and annualised relapse rate, the manufacturer used results from its mixed treatment comparison. The manufacturer applied these treatment effects only to patients with relapsing-remitting multiple sclerosis because it assumed that patients with secondary progressive multiple sclerosis stop treatment. The economic model did not allow patients to switch treatments, so they remained on their original treatment until disease progression. In the absence of evidence, the manufacturer also chose to assume that the treatment has no effect on the disease developing to secondary progressive multiple sclerosis. The manufacturer noted that this assumption was supported in previous NICE technology appraisals of multiple sclerosis ('Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis' [NICE technology appraisal guidance 254]). The model assumes that the treatment effect diminishes over time and introduces a waning effect after 2 years. The manufacturer explained that because of a lack of long-term data on the clinically effectiveness of dimethyl fumarate it applied a similar approach to that used by Committee in a previous NICE technology appraisal of multiple sclerosis ('Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis' [NICE technology appraisal guidance 254]). Treatment was administered until a patient's disease progresses to secondary progressive multiple sclerosis, patients die, or stop because of adverse reactions. After stopping treatment, the manufacturer assumed that patients follow the natural history of disease progression.

6.5 To estimate the probabilities for all-cause mortality in the multiple sclerosis population, the manufacturer took England and Wales national mortality data and adjusted it for patients with multiple sclerosis by age and EDSS score using mortality multipliers from a Danish population

diagnosed with multiple sclerosis from 1948 onward reported in Pokorski et al. (1997). Mortality was assumed to be the same in patients with relapsing-remitting multiple sclerosis and patients with secondary progressive multiple sclerosis.

6.6 Resource use and costs in the economic model dependended on a patient's EDSS score, whether they had relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis, and whether they were in relapse. The unit costs for each of the drugs and their administration were taken from the 'British National Formulary 64' and 'NHS Reference Costs 2011-2012'. The cost of dimethyl fumarate in the model included the patient access scheme discount. Resource use and costs associated with monitoring patients on treatment were based on the licenced indications presented in its summary of product characteristics of the drugs. The manufacturer took resource use data for managing the disease from the UK multiple sclerosis survey that included 115 difference healthcare resources. Using a regression analysis to model the UK multiple sclerosis survey data, the manufacturer estimated a mean annual cost for each EDSS score in patients with relapsing-remitting multiple sclerosis and patients with secondary progressive multiple sclerosis (see Table 2), and the mean cost per relapse independent of the clinical form of multiple sclerosis (that is, £2028 per relapse in people with relapsing-remitting multiple sclerosis and £2028 per relapse in people with secondary progressive multiple sclerosis).

Table 2: Costs by EDSS score used in the model (£) [page 212, table 70, manufacturer's submission]

Disease type	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9
RRMS	903	939	688	3,765	1,824	3,094	4,130	10,871	26,478	21,187
SPMS	1,217	1,254	1,002	4,079	2,138	3,409	4,444	11,185	26,793	21,502

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

[redacted]

6.7 To estimate health-related quality of life, the manufacturer used pooled EQ-5D data from the DEFINE and CONFIRM trials for the EDSS health states for relapsing-remitting multiple sclerosis. The manufacturer estimated the utility values for secondary progressive multiple sclerosis using the differences between utility values for relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis from the UK Multiple Sclerosis Survey (see Table 3). The manufacturer also subtracted the difference between utility for relapse and no relapse for each EDSS state as reported in the UK Multiple Sclerosis Survey from its EQ-5D trial data to estimate the utility values for patients with relapse (see Table 3). The manufacturer's economic model also incorporated caregiver's disutility for each EDSS score, in line with estimates from previous NICE technology appraisals of multiple sclerosis ('Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis' [NICE technology appraisal guidance 254], 'Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis' [NICE technology appraisal guidance 127]). The maximum disutility is assumed to be 0.14 for a caregiver of a person with multiple sclerosis with an EDSS score of 9.

Table 3: Utility scores used in the manufacturer's economic model [page 201, table 63, manufacturer's submission]

EDSS health state	RRMS		SPMS	
	No relapse	Relapse	No relapse	Relapse
0	0.8752	0.8660	0.8315	0.8223
1	0.8342	0.8250	0.7905	0.7814
2	0.7802	0.7710	0.7365	0.7274
3	0.6946	0.6855	0.6509	0.6418
4	0.6253	0.6161	0.5816	0.5725
5	0.5442	0.5350	0.5005	0.4913
6	0.4555	0.4463	0.4118	0.4027
7	0.3437	0.3346	0.3000	0.2909
8	0.0023	-0.0068	-0.0413	-0.0505
9	-0.1701	-0.1793	-0.2138	-0.2229

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

6.8 The economic model included costs and disutility values associated with adverse reactions. The manufacturer included only adverse reactions reported in the trials that either had an incidence of 5% or more, or the absolute incidence in the dimethyl fumarate arm was 3% higher than in the placebo arm. The manufacturer took resource use and costs for each adverse reaction from published sources and validating them by clinical expert opinion. Disutility values were based on clinical expert opinion, published sources when available or the manufacturer's assumption.

6.9 The manufacturer presented deterministic pairwise incremental cost-effectiveness ratios (ICERs) for dimethyl fumarate with the patient access scheme compared with each of the treatments included in its economic model (Table 4). The manufacturer updated its economic model during the factual accuracy check of the ERG report to include the prices from the NHS Risk Sharing Scheme for beta interferons and glatiramer acetate in its base case analysis; therefore, the results presented in the manufacturer's submission have been superseded. Dimethyl fumarate dominated Avonex (that is, dimethyl fumarate gave more QALYs and cost less than Avonex), the manufacturer estimated incremental cost savings

of £223 and 0.194 incremental QALYs gained. For dimethyl fumarate compared with Rebif-22, the manufacturer estimated incremental costs of £6093 and 0.286 incremental QALYs gained with an ICER of £21,341 per QALY gained. For dimethyl fumarate compared with Rebif-44, the manufacturer estimated incremental costs of £2592 and 0.163 incremental QALYs gained with an ICER of £15,909 per QALY gained. For dimethyl fumarate compared with Betaferon, dimethyl fumarate dominated Betaferon, the manufacturer estimated incremental cost savings of £2834 and 0.386 incremental QALYs gained. For dimethyl fumarate compared with glatiramer acetate, the manufacturer estimated incremental costs of £6516 and 0.331 incremental QALYs gained with an ICER of £19,716 per QALY gained. The patient access scheme price for fingolimod was not included in the manufacturer's base-case analysis because it is not publically available and the manufacturer of fingolimod did not provide the patient access scheme to the manufacturer of dimethyl fumarate. Assuming a 35% reduction in the list price of fingolimod, dimethyl fumarate dominated fingolimod, the manufacturer estimated incremental cost savings of £18,347 and 0.264 incremental QALYs gained. For dimethyl fumarate compared with natalizumab, the manufacturer estimated incremental cost savings of £46,256 and an incremental QALY loss of 0.103 leading to savings of £448,729 per QALY lost.

[redacted]

Table 4: Manufacturer' base-case pairwise ICERs for dimethyl fumarate

Comparator	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (cost/QALY)
Glatiramer acetate	£231,455	5.453	£6516	0.331	£19,716
Rebif-22	£231,878	5.783	£6093	0.286	£21,341
Rebif-44	£235,380	5.621	£2592	0.163	£15,909
Dimethyl fumarate*	£237,971	5.783			
Avonex	£238,194	5.589	(£223)	0.194	Dominated
Betaferon	£240,805	5.398	(£2834)	0.386	Dominated
Fingolimod	£256,319	5.519	(£18,347)	0.264	Dominated
Natalizumab	£284,227	5.887	(£46,256)	(0.103)	(£448,729) less costly and less effective

Brackets indicate a negative number. * intervention

6.10 The manufacturer explored parameter and structural uncertainty in its economic model by presenting the results of univariate sensitivity analyses, two-way sensitivity analyses and scenario analyses. The results from the univariate sensitivity analyses suggested the manufacturer's economic model was most sensitive to changes in the effect of treatment on the disability progression rate (ICERs increased when the effect of dimethyl fumarate was reduced by 20%, or the effect of the comparator was increased by 20%). The manufacturer commented that its scenario analyses indicated that its economic model is robust to most of the structural assumptions. The results from the scenario analyses were most sensitive to changes in the time horizon. In its scenario analyses, the manufacturer varied the price of fingolimod by reducing its list price in 5% increments. It estimated that dimethyl fumarate dominated fingolimod up to a 60% decrease in its list price.

6.11 The manufacturer also presented probabilistic ICERs. Dimethyl fumarate dominated Betaferon and fingolimod (with a 35% reduction in list price of fingolimod). For dimethyl fumarate compared with Rebif-22, the manufacturer estimated an ICER of £30,898 per QALY gained. For dimethyl fumarate compared with Rebif-44, the manufacturer estimated

[redacted]

an ICER of £23,408 per QALY gained. For dimethyl fumarate compared with Avonex, the manufacturer estimated an ICER of £2573 per QALY gained. For dimethyl fumarate compared with glatiramer acetate, the manufacturer estimated an ICER of £30,331 per QALY gained. For dimethyl fumarate compared with natalizumab, the manufacturer estimated incremental cost savings and an incremental QALY loss leading to savings of £610,134 per QALY lost.

ERG comments on the cost effectiveness data

6.12 The ERG noted that the economic model structure adopted by the manufacturer is the common approach to modelling the disease pathway of multiple sclerosis in NICE technology appraisals. It stated that including improvement to lower EDSS states reflects the actual experience of patients in the trials of dimethyl fumarate and the experience of people with relapsing-remitting multiple sclerosis. Although sustaining disability progression for 6 months may be more closely associated with permanent progression, the ERG noted that the use of 3 month sustained disability progression outcome data in the manufacturer's economic model was reasonable because patients could regress to lower EDSS health states. The ERG commented that the economic model predictions of the patients across the EDSS health states seem reasonable compared with the distribution of dimethyl fumarate patients across the EDSS states within the time period of the trials.

6.13 The ERG preferred the manufacturer's ICERs calculated from the probabilistic sensitivity analysis compared with the deterministic ICERs because the economic model is non-linear. However, the ERG noted that the manufacturer had not assigned probability distributions to a number of parameters including the parameter accounting for treatment waning over time and the annual risk of stopping treatment. The ERG explained that these 2 parameters have a significant effect on the estimated ICERs because disease progression is the key driver of the economic model.

The ERG noted that the main driver of the economic model was the relative risk of 3 month disability progression but it did not explore any analyses around this parameter because it felt that the manufacturer's mixed treatment comparison and probability distributions were adequate for this parameter. Although the ERG noted that a fixed-effects mixed treatment comparison may underestimate the uncertainty in the treatment effect, and therefore the uncertainty in the cost-effectiveness estimates of dimethyl fumarate may also be underestimated. It concluded that although the probabilistic results are more meaningful and represent a less biased approximation of the ICER compared with deterministic results, the full impact of the uncertainty around the ICER has not been completely accounted for.

6.14 The ERG's base case deterministic pairwise ICERs were all within £100 of those presented by the manufacturer during its factual accuracy check of the ERG report, and are therefore not presented here, for further details see the ERG addendum The ERG also presented base case incremental results. In an incremental analysis, dimethyl fumarate is compared with all treatments and the treatments are ordered by increasing costs. In its incremental analysis using hazard ratios as the outcome measure for 3 month disability progression at 2 years, the ERG estimated that the:

- Deterministic ICER of dimethyl fumarate to be £21,414 compared with Rebif-22.
- Probabilistic ICER of dimethyl fumarate to be £31,244 compared with Rebif-22.

The ERG undertook several exploratory analyses (see sections 6.15 to 6.21). Because running probabilistic analyses in the manufacturer's economic model was time consuming, the ERG only estimated deterministic pairwise ICERs.

6.15 The ERG considered that the resource use relating to neurology visits in the manufacturer's economic model were: too high in year 1 for beta interferons, too low in year 1 for natalizumab, and too low after year 1 for dimethyl fumarate and fingolimod. It also chose to explore a scenario assuming that the cost of a neurology visit was equal to the cost of visiting a neurologist specialist because the manufacturer assumed that the cost of a neurology visit was equal to the cost of a day case admission. Two other resource use estimates for monitoring people with relapsing-remitting multiple sclerosis in the manufacturer's economic model were revised by the ERG: including annual MRI scans for patients taking natalizumab and including nurse visits for patients taking injectable treatments. Using alternative monitoring resource assumptions, the ERG estimated that its base case ICER increased from £21,414 to between £21,419 and £28,973 for dimethyl fumarate compared with Rebif-22. For further details see pages 115–117 of the ERG report and ERG addendum.

6.16 The ERG commented that the baseline distribution of patients across EDSS health states is based on the trials of dimethyl fumarate in the manufacturer's economic model. The ERG recognised that the population in the dimethyl fumarate trials differs from the prevalent relapsing-remitting multiple sclerosis population because the trials' inclusion criteria required patients to have had a relapse within the 12 months before randomisation (see section 4.12). However, it acknowledged that the trial population is the closest to the population specified in the final scope for which evidence is available, and because reducing relapses is an aim of treatment, prescribing treatment to only those patients suffering from relapse is reasonable. For further details see pages 118–119 of the ERG report and ERG addendum.

6.17 The ERG explored alternative assumptions around the rates of stopping treatment. Changing the relative risks of stopping treatment from those estimated in the mixed treatment comparison to 50% and 0% for both

[redacted]

comparators after 2 years of treatment estimated an increase to the ERG's base case ICER for dimethyl fumarate compared with Rebif-22 from £21,414 to £23,378 and £23,292 per QALY gained respectively. The ICER for dimethyl fumarate compared with glatiramer acetate increased above £30,000 per QALY gained when using the lower confidence intervals of the relative risks of stopping treatment. The ERG commented that when patients stop their starting treatment in the manufacturer's economic model they take placebo or 'best supportive care', and therefore progress more quickly through the EDSS health states. Switching from treatment to no treatment reduces costs to a greater extent than it reduces QALYs, therefore the more patients that stop treatment, the more cost effective the treatment appears. The ERG raised the concern that if best supportive care were specified in the scope as one of the comparators, the ICER of dimethyl fumarate compared with an active treatment would never be less than the ICER of dimethyl fumarate compared with best supportive care. However, in clinical practice the ERG considered that patients who stop treatment because of adverse reactions will take another active treatment if an alternative (with a differing side effect profile) is available. Furthermore, it noted patients who progress to secondary progressive multiple sclerosis are likely to take some form of active treatment but this scenario has not be included in the manufacturer's economic model due to a lack of available data. For further details see pages 119–121 of the ERG report and ERG addendum.

6.18 The ERG noted that using data from the trials (when available) to model the natural history of the disease was largely appropriate. It explained that it was not able to assess whether the London Ontario population reflected the population specified in the final scope because little has been published about this dataset However, the ERG stated that in the absence of trial data the manufacturer used the best available evidence to model

the natural history of the disease. For further details, see pages 121–122 of the ERG report and ERG addendum.

6.19 The ERG considered that it was appropriate for the manufacturer to use utility values estimated from the trials of dimethyl fumarate. However, it noted that by using the utility values from the trials as a proxy for 'people with relapsing-remitting multiple sclerosis without relapse' in its economic model, the manufacturer may have underestimated the health-related quality of life of these patients because some of the patients included in the trials will have been in relapse. The ERG explored this uncertainty by incorporating utility values from 2 other sources based on the UK Multiple Sclerosis Survey in its economic model because the absolute utility values were slightly higher compared with the trial data (firstly, using the utility values as reported in Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis' [NICE technology appraisal guidance 127] and secondly the utility values estimated from a multivariate linear regression analysis of the UK Multiple Sclerosis Survey in Orme et al. 2007). However, the ERG noted that only 35.5% of the UK Multiple Sclerosis Survey population had relapsing-remitting multiple sclerosis. It was also concerned with the utility values in all sources because the decrements calculated between secondary progressive multiple sclerosis and relapsing-remitting multiple sclerosis and between relapse compared to no relapse were based on a population that did not entirely reflect the scope of the appraisal. For dimethyl fumarate compared with Rebif-22, the ERG estimated that its base case ICER changed from £21,414 to between £18,700and £22,144per QALY gained when using the utility values from Omre et al. (2007) and NICE technology appraisal 127 respectively. For further details, see pages 122–123 of the ERG report and ERG addendum.

6.20 The ERG considered the different EDSS state costs for people with relapsing-remitting multiple sclerosis and people with secondary progressive multiple sclerosis appropriate. It was aware of 3 sources

reporting costs by EDSS states that used the resource use data from the UK Multiple Sclerosis Survey (including the source used in the manufacturer's economic model). However, despite using the same resource use data, the 3 sources estimated different costs. The ERG explained that the variation between estimates may be because each source used different unit costs and only 1 of the sources separated medical and non-medical costs. It stated it was unclear which of the 3 sources was the most appropriate but these differing estimates of EDSS health state costs did not have a significant impact on the ICERs. For dimethyl fumarate compared with Rebif-22, the ERG estimated that its base case ICER changed from £21,414 to between £17,239 and £21,377 per QALY gained. The ERG judged the cost per relapse in the manufacturer's economic model of £2208 to be too high after receiving advice from clinicians that only 20% of relapses need hospitalisation. When the ERG varied the cost per relapse between £3309 and £280 the ICER changed from £21,414 to £18,660 and £26,074 per QALY gained respectively, for dimethyl fumarate compared with Rebif-22. For further details see pages 123–126 of the ERG report and ERG addendum.

6.21 Although the manufacturer's economic model did not include the relative risks of adverse reactions from its mixed treatment comparison in its economic model, the ERG stated that the manufacturer's approach to informing the incidence of adverse reactions was reasonable. Using the relative risk of adverse reactions from the manufacturer's mixed treatment comparison, or assuming no adverse reactions, the ERG estimated that its base case ICER changed from £21,414 to £26,683 or to £24,869 per QALY gained respectively, for dimethyl fumarate compared with Rebif-22. The ERG also explored revised disutilities for influenza and flu-like symptoms because the manufacturer's estimate seemed too high. Updating these disutilities had marginal impact to the incremental cost-effectiveness results. For further details, see pages 126–128 of the ERG report and ERG addendum.

[redacted]

7 Equalities issues

7.1 One consultee highlighted that children should be considered; however, the clinical trials and anticipated marketing authorisation of dimethyl fumarate includes only adults. NICE can appraise, and issue guidance on, a technology only within its marketing authorisation.

7.2 No further equalities issues were highlighted at the scoping workshop or during consultation of the draft scope.

8 Innovation

8.1 The manufacturer and a professional group commented that the oral formulation is innovative. The manufacturer stated that oral dimethyl fumarate offers greater efficacy compared with the first-line self-injectable beta-interferons and glatiramer acetate, and a more favourable safety profile compared with intravenous natalizumab and oral fingolimod.

8.2 The manufacturer noted dimethyl fumarate is the first treatment for people with relapsing-remitting multiple sclerosis that activates the nuclear factor erythroid-derived 2-like 2 (Nrf2) pathway. The professional group supported that its mechanism of action is innovative because it has dual immunomodulatory mechanisms, one anti-inflammatory and the other neuroprotective. The manufacturer commented that because dimethyl fumarate is absorbed in the small intestine, it avoids potential gastric irritation and provides optimal delivery into the bloodstream.

8.3 The manufacturer suggests that the use of dimethyl fumarate may result in potential significant and substantial health-related benefits that are unlikely to be captured in the QALY calculation. Patients receiving beta-interferons or glatiramer acetate often experience treatment anxiety as a result of self-injection, and may find their administration schedule burdensome. The manufacturer highlighted research that estimated that up to 25% of patients receiving beta-interferons or glatiramer acetate do

not adhere to treatment. Of these patients, 32% noted injection related reasons for non-adherence. The manufacturer concluded that providing an oral therapy for people with relapsing-remitting multiple sclerosis is likely to improve adherence, and therefore may result in improved clinical outcomes. No evidence base is available suggesting a link between adherence and clinical outcomes in multiple sclerosis, but the manufacturer noted this has been extensively researched in people with HIV. However, the professional and patient groups suggested that having to adminster dimethyl fumarate twice daily may also cause patients not to adhere to treatment when compared with once daily treatment options, and therefore there is uncertainty whether the outcomes achieved in the clinical trials can be replicated in clinical practice.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis. NICE technology appraisal guidance 254 (2012).
- Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. NICE technology appraisal guidance 127 (2007).
- Management of multiple sclerosis in primary and secondary care. NICE clinical guideline 8 (2003).
- Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. NICE technology appraisal guidance 32 (2002).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Teriflunomide for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication January 2014.
- Alemtuzumab for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication April 2014.
- Laquinimod for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication October 2014.
- Cladribine for the treatment of relapsing-remitting multiple sclerosis. Suspended NICE technology appraisal.