

Dimethyl fumarate for treating relapsing-remitting multiple sclerosis

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Guidance

- 1.1 Dimethyl fumarate is recommended as an option for treating adults with active relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), **only if**:
- they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis **and**
 - the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.
- 1.2 People currently receiving treatment initiated within the NHS with dimethyl fumarate that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

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 a UK marketing authorisation for 'the treatment of adult patients with relapsing-remitting multiple sclerosis'.
- 2.2 The summary of product characteristics lists the following adverse reactions for dimethyl fumarate: 'gastroenteritis, lymphopenia, leukopenia, 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 summary of product characteristics.
- 2.3 Dimethyl fumarate is taken orally. The recommended dosage is 120 mg twice daily in the first week of treatment and 240 mg twice daily thereafter. 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 prices of a pack of 120-mg tablets (14 tablets per pack) and 240-mg tablets (56 tablets per pack) are £343 and £1373 respectively (excluding VAT; manufacturer's submission). 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 The manufacturer's submission

The Appraisal Committee ([section 8](#)) considered evidence submitted by the manufacturer of dimethyl fumarate and a review of this submission by the Evidence Review Group (ERG; [section 9](#)).

Clinical effectiveness

- 3.1 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.
- 3.2 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 geographical region and randomised in a 1:1:1 ratio to dimethyl fumarate 240 mg twice daily (n=410), dimethyl fumarate 240 mg 3 times 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 geographical region and randomised in a 1:1:1:1 ratio to dimethyl fumarate 240 mg twice daily (n=359), dimethyl fumarate 240 mg 3 times 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 the study drug or withdrew consent. For dimethyl fumarate, only data relating to the licensed dosage (240 mg twice daily) were presented in the manufacturer's submission.
- 3.3 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, had an Expanded Disability Status Scale (EDSS) score of between 0

and 5 inclusive (the EDSS ranges from 0 to 10 in 0.5-unit increments, higher scores representing higher levels of disability) and had either had at least 1 relapse during the previous year and a previous MRI scan showing lesions consistent with multiple sclerosis, or had 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 were white (79% in DEFINE, 84% in CONFIRM) and were women (74% in DEFINE, 70% in CONFIRM). The mean age of patients was 38.5 years and 37.3 years in the DEFINE and CONFIRM trials respectively. In the DEFINE trial, 29 patients were treated at 7 UK centres. The CONFIRM trial did not include any UK centres.

- 3.4 The primary outcome measures in the trials were the proportion of patients with a relapse at 2 years (DEFINE) and the annualised relapse rate at 2 years (CONFIRM). Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting 24 hours or longer, and with new objective neurological findings. An intention-to-treat population was the primary population for the analysis of efficacy outcomes in both trials adjusted for age, EDSS score, number of relapses in the year before randomisation and geographical region using proportional hazards regression in the DEFINE trial, and negative binomial regression in the CONFIRM trial. In the DEFINE trial, the proportion of patients with a relapse at 2 years was statistically significantly reduced with dimethyl fumarate compared with placebo (27% versus 46%; hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.40 to 0.66). In the CONFIRM trial, the 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 difference between dimethyl fumarate and placebo was statistically significant. 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.

- 3.5 Secondary outcomes reported annualised relapse rate at 2 years (DEFINE), the proportion of patients with a relapse at 2 years (CONFIRM), and in both trials, progression of disability on the EDSS and number of MRI lesions (in a subset of patients) at 2 years. In the DEFINE trial, the annualised relapse rate at 2 years was statistically significantly reduced with dimethyl fumarate compared with placebo (0.17 compared with 0.36; 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 statistically significantly reduced with dimethyl fumarate compared with placebo (29% compared with 41%; HR 0.66, 95% CI 0.51 to 0.86). Patients taking dimethyl fumarate had a statistically significantly reduced risk of disability progression sustained for 3 months at 2 years compared with those taking placebo in the DEFINE trial (16% compared with 27%; HR 0.62, 95% CI 0.44 to 0.87). However, in the CONFIRM trial, the difference in the risk of disability was not statistically significant (13% compared with 17%; HR 0.79, 95% CI 0.52 to 1.19). The manufacturer suggested that the 3-month disability progression results in the CONFIRM trial may have been affected by the fact that the proportion of patients censored (whose disability may or may not have progressed) was higher in the placebo arm than in the dimethyl fumarate arm. It explained that patients were censored if they withdrew from the study or switched treatments before 3-month progression could be confirmed. Analyses of disability progression sustained for 6 months at 2 years comparing dimethyl fumarate with placebo in DEFINE (HR 0.77, 95% CI 0.52 to 1.14) and CONFIRM (HR 0.62, 95% CI 0.37 to 1.03) were presented in the European Public Assessment Report, and these differences were not statistically significant. The number of lesions on T1- and T2-weighted and gadolinium-enhancing MRI at 2 years was statistically significantly lower with dimethyl fumarate than with placebo in the DEFINE and CONFIRM trials.
- 3.6 The manufacturer presented results for the pre-specified subgroup analyses for the DEFINE and CONFIRM trials in its submission. It stated that the results (treatment effect) of these analyses were generally consistent with the results for the overall population. The DEFINE trial results were similar for patients who had not had treatment for multiple sclerosis before (treatment-naive); (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;

3-month disability progression at 2 years: 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) showing statistically significant differences between patients taking dimethyl fumarate and placebo. However, for the 3-month disability progression at 2 years outcome, disability progression was not statistically significantly reduced with dimethyl fumarate compared with placebo for the treatment-experienced subgroup (HR 0.83, 95% CI 0.54 to 1.29). The manufacturer also noted that the CONFIRM trial results were similar for treatment-naive patients (annualised relapse rate: RR 0.64, 95% CI 0.44 to 0.95; proportion relapsed: HR 0.73, 95% CI 0.51 to 1.05; 3-month disability progression at 2 years: HR 0.56, 95% CI 0.30 to 1.03) and for 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 at 2 years: HR 1.07, 95% CI 0.60 to 1.89) showing statistically significant differences between patients taking dimethyl fumarate and placebo for all outcomes except for 3-month disability progression at 2 years in patients who had already had treatment. No tests of interaction were presented by the manufacturer.

- 3.7 Both trials measured health-related quality-of-life using the global well-being visual analogue scale (VAS; which assesses a patient's global well-being on study treatment on a linear scale, with 0 as 'poor' and 100 as 'excellent'), 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 statistically significantly better health-related quality-of-life compared with those randomised to placebo when measured by the mean change in: global well-being VAS from baseline (0.4 compared with -4.0; $p=0.0031$), the physical component score of the SF-36 from baseline (0.5 compared with -1.4; $p<0.001$), 6 of 8 SF-36 subscales from baseline, and EQ VAS from baseline (-0.3 compared with -4.2; $p<0.001$). In the CONFIRM trial, patients randomised to dimethyl fumarate showed a statistically significantly better health-related quality-of-life compared with those randomised to placebo when measured by the mean change in: global well-being VAS from baseline (0.3 compared with -3.9; $p<0.001$), the physical component score of the

SF-36 from baseline (0.5 compared with -0.7; $p=0.0217$), and 3 of 8 SF-36 subscales from baseline.

- 3.8 The manufacturer reported that the overall incidence of adverse reactions was similar in 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% in DEFINE and 5% compared with 2% in CONFIRM), upper abdominal pain (10% compared with 7% in DEFINE and 10% compared with 5% in CONFIRM), nausea (13% compared with 9% in DEFINE and 11% compared with 8% in CONFIRM) and vomiting (10% compared with 6% in DEFINE 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. The percentages of patients stopping treatment because of adverse reactions were 16% of those taking dimethyl fumarate and 13% of those taking placebo in the DEFINE trial, and 12% of those taking dimethyl fumarate and 10% of those taking placebo in the CONFIRM trial. The manufacturer reported that the incidence of serious adverse reactions in patients taking dimethyl fumarate was comparable to patients taking placebo (18% compared with 21% in DEFINE and 17% compared with 22% in CONFIRM).
- 3.9 The manufacturer presented the results of both a fixed-effects and a random-effects meta-analysis of the efficacy and safety outcomes of the DEFINE and CONFIRM trials. It estimated that dimethyl fumarate was statistically significantly better than placebo for all efficacy outcomes analysed including disability progression sustained for 3 months and for 6 months, both at 2 years. The manufacturer's meta-analysis also estimated that patients taking dimethyl fumarate experienced statistically significantly more gastrointestinal events, flushing and skin reactions compared with those taking placebo or glatiramer acetate. It estimated no statistically significant differences in the number of withdrawals for any reason between treatments, but that statistically significantly more patients taking dimethyl fumarate withdrew because of adverse reactions compared with those taking placebo or glatiramer

acetate.

- 3.10 To estimate the relative effectiveness of dimethyl fumarate compared with the comparators defined in the scope, the manufacturer conducted a mixed treatment comparison of 27 trials using a fixed-effects frequentist approach that assessed outcomes including annualised relapse rate, proportion of relapsing patients at 24 months, and confirmed disability progression sustained for 3 months and for 6 months, both at 2 years. The following comparators were included in the manufacturer's mixed treatment comparison: beta interferon-1a (Avonex, Rebif-22 and Rebif-44), beta interferon-1b (Betaferon), glatiramer acetate, fingolimod, natalizumab and placebo.
- 3.11 The manufacturer presented results of the mixed treatment comparison unadjusted for covariates. The manufacturer did a covariate analysis that showed that the chosen covariates had little or no impact on the outcomes of interest, although the baseline relapse rate was found to be a significant covariate for the annualised relapsed rate outcome. The manufacturer's unadjusted mixed treatment comparison suggested that dimethyl fumarate statistically significantly reduces the annualised relapse rate and the proportion of patients with relapses at 2 years compared with placebo, glatiramer acetate and all beta interferons. The manufacturer's mixed treatment comparison also suggested dimethyl fumarate statistically significantly reduces disability progression sustained for 3 months at 2 years compared with placebo. No statistically significant differences were estimated between dimethyl fumarate and any comparator, including placebo, for disability progression sustained for 6 months at 2 years. The manufacturer labelled the effect size and credible intervals from its mixed treatment comparison as academic in confidence, and therefore they cannot be presented here. 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.

Cost effectiveness

- 3.12 The manufacturer did not identify any published studies of the 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 9 treatments: dimethyl fumarate, a beta interferon-1a treatment (Avonex, Rebif-22 or Rebif-44), beta interferon-1b (Betaferon, Extavia), glatiramer acetate, fingolimod or natalizumab. The manufacturer conducted the economic analysis from an NHS and personal social services perspective and chose a time horizon of 30 years. Costs and health effects were discounted at an annual rate of 3.5% and a half-cycle correction was applied.

- 3.13 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 estimated disease progression through 21 health states defined by EDSS scores (ranging from 0 to 9.5), which cover disability in patients with relapsing-remitting multiple sclerosis (10 states), patients with secondary progressive multiple sclerosis (10 states) and death. In each cycle of the model, a patient with relapsing-remitting multiple sclerosis could move to a higher or lower EDSS state or remain in the same state. Patients could also advance from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis, but could not subsequently move back to relapsing-remitting disease. Only patients with relapsing-remitting multiple sclerosis and an EDSS score of 6 or less were assumed to receive disease-modifying treatment in the model.
- 3.14 Patient baseline characteristics were pooled from the DEFINE and CONFIRM trials. The probabilities of changing EDSS state or having a relapse (fixed for each EDSS state) were 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 and including an EDSS score of 7, and using a longitudinal data set of patients with multiple sclerosis in London 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:

- progressing from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis (by EDSS score) and
- progressing within the secondary progressive multiple sclerosis states.

The pooled baseline trial data gave the natural history of relapses by EDSS score in patients with an EDSS score of up to and including 5. The natural history of relapses by EDSS score in patients with an EDSS score of more than 5 was estimated by the manufacturer using data from Patzold et al. (1982) and the UK Multiple Sclerosis Survey because the sample sizes of patients with an EDSS score of more than 5 from the trials were small.

- 3.15 To estimate disability progression and the annualised relapse rate of each treatment compared with placebo, the manufacturer used results from its mixed treatment comparison (that is, using the 'disability progression sustained for 3 months at 2 years' and 'annualised relapse rate' data). The manufacturer applied 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 progression to EDSS score of 7 or more, because of adverse reactions, or conversion to secondary progressive multiple sclerosis. Because there was no evidence, the manufacturer also assumed that the treatment has no effect on disease progression to secondary progressive multiple sclerosis. The manufacturer noted that this assumption was adopted in [Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis](#) (NICE technology appraisal guidance 254). The model assumed that the treatment effect diminishes over time (waning) to 75% after 2 years and to 50% after 5 years. The manufacturer explained that because of a lack of long-term data on the clinical effectiveness of dimethyl fumarate it applied a similar approach to that adopted by the Committee in NICE technology appraisal guidance 254. The manufacturer assumed that

patients followed the natural history of disease progression after stopping treatment.

- 3.16 To estimate the probabilities for all-cause mortality in the multiple sclerosis population, the manufacturer took England and Wales national mortality data and adjusted 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 secondary progressive multiple sclerosis. The manufacturer presented the results of a scenario analysis that explored setting the rate of mortality in people with relapsing-remitting multiple sclerosis equal to the rate of mortality in the general population of England and Wales.
- 3.17 Resource use and costs in the economic model depended on a patient's EDSS score, on whether they had relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis, and on whether they were in relapse. The unit costs for each of the drugs and their administration were all originally taken from the 'British National Formulary 64' and 'NHS Reference Costs 2011/12'. 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. The cost of dimethyl fumarate in the model included the patient access scheme. Resource use and costs associated with monitoring patients on treatment were based on the licensed indications presented in the summaries of product characteristics of the drugs. The manufacturer took resource-use data for managing the disease from a regression analysis of data from the UK Multiple Sclerosis Survey that included 115 different healthcare resources. 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, and the mean cost per relapse independent of the clinical form of multiple sclerosis (that is, £2028 per relapse both in people with relapsing-remitting multiple sclerosis and people with secondary progressive multiple sclerosis).

- 3.18 To estimate health-related quality-of-life, the manufacturer used pooled EQ-5D data from the DEFINE and CONFIRM trials for the EDSS 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. 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. The manufacturer's economic model also incorporated carer's disutility for each EDSS score, in line with estimates from [Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis](#) (NICE technology appraisal guidance 254) and [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 carer of a person with multiple sclerosis with an EDSS score of 9.
- 3.19 The economic model included costs and disutility values associated with adverse reactions. The manufacturer only included adverse reactions reported in the trials when the incidence was 5% or higher, or when 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 validated them by clinical expert opinion. Disutility values were based on clinical expert opinion, published sources when available or the manufacturer's assumption.
- 3.20 The manufacturer presented deterministic pairwise incremental cost-effectiveness ratios (ICERs) for dimethyl fumarate compared with each of the treatments included in its economic model. 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 publicly 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 in the active relapsing-remitting multiple sclerosis population: 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.

- 3.21 The manufacturer explored parameter and structural uncertainty in its economic model by presenting the results of univariate sensitivity analyses, 2-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 in the active relapsing-remitting multiple sclerosis population unless fingolimod's list price is decreased by more than 60%.
- 3.22 The manufacturer also presented results from probabilistic analyses in the active relapsing-remitting multiple sclerosis population. Dimethyl fumarate dominated Betaferon and fingolimod (with a 35% reduction in

the 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 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 clinical effectiveness

3.23 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 reflect people with relapsing-remitting multiple sclerosis who meet the Association of British Neurologists' 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 that:

- Patients in the NHS risk-sharing scheme (patients taking beta interferon or glatiramer acetate who need to meet the Association of British Neurologists' prescribing criteria to be eligible for treatment) have a mean of 2.9 relapses in the previous 2 years whereas the ERG's clinical advisers suggested that the annualised relapse rate in the whole population with relapsing-remitting multiple sclerosis generally is approximately 0.8.
- The baseline annualised relapse rates in the DEFINE and CONFIRM trials were 1.3 and 1.4 respectively (which reflected the inclusion criterion requiring patients 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 the prevalent relapsing-remitting multiple sclerosis population was unknown. However, the ERG commented that the trial populations broadly represented people with relapsing-remitting multiple sclerosis treated with disease-modifying therapy in UK clinical practice for age, sex and disease

duration, and did not consider the differences between the trial populations and the UK clinical population to be clinically significant.

- 3.24 The ERG stated that 3-month disability progression was used as an outcome measure in Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis (NICE technology appraisal guidance 254). However, this is not consistent with the European Medicines Agency's draft guideline on the clinical investigation of medicinal products for the treatment of multiple sclerosis 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 that some uncertainty remained regarding the effect of dimethyl fumarate on disability progression.
- 3.25 The ERG stated that the rates of adverse reactions and serious adverse reactions for patients taking dimethyl fumarate were similar to those for placebo. The ERG noted that higher incidences of flushing and gastrointestinal events were reported for dimethyl fumarate, but these appeared to be confined mainly to the first 3 months of treatment. It was unclear whether this was also the case for skin reactions.
- 3.26 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 was considerable uncertainty regarding the long-term efficacy and safety of dimethyl fumarate.

- 3.27 The ERG commented that the manufacturer's mixed treatment comparison included all relevant trials. It noted that these trials appeared 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 meaningful. However, the ERG concluded the level of heterogeneity between trials was not sufficient to make the comparisons unreasonable.

3.28 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 more appropriate for assessing the annualised relapse rate than a fixed-effects model because the network included a sufficient number of trials. The ERG noted that the estimated confidence intervals for the annualised relapse rate outcome may therefore have been slightly underestimated (that is, too narrow).

3.29 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 those defined in the comparator drugs' marketing authorisations. However, the ERG concluded that because the manufacturer did not analyse patients with highly active relapsing-remitting multiple sclerosis or rapidly evolving severe relapsing-remitting multiple sclerosis, the relative effectiveness of dimethyl fumarate compared with fingolimod and natalizumab was unknown in these subgroups respectively.

ERG comments on the cost effectiveness

3.30 The ERG confirmed that the economic model structure adopted by the manufacturer was structurally similar to that used in previous NICE technology appraisals of multiple sclerosis. It stated that including improvement to lower EDSS states reflected the actual experience of

patients in the trials of dimethyl fumarate and the experience of people with relapsing-remitting multiple sclerosis generally. 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' disease could improve to lower EDSS states. The ERG commented that the economic model predictions for the patients across the EDSS states seemed reasonable compared with the distribution of dimethyl fumarate patients across the EDSS states within the time period of the trials.

- 3.31 The ERG preferred the manufacturer's ICERs calculated from the probabilistic sensitivity analysis to 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 hazard ratio 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. However, the ERG stated 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 were more meaningful and represented a less biased approximation of the ICER compared with deterministic results, the full impact of the uncertainty around the ICER had not been completely accounted for.
- 3.32 The ERG's exploratory analyses resulted in base-case deterministic pairwise ICERs 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 using hazard ratios as the outcome measure for 3-month disability progression at 2 years, which

showed that:

- the deterministic ICER per QALY gained for dimethyl fumarate compared with Rebif-22 was £21,414
- the probabilistic ICER per QALY gained for dimethyl fumarate compared with Rebif-22 was £31,244.

The ERG undertook several further exploratory analyses (see sections 3.33 to 3.37). Because running probabilistic analyses in the manufacturer's economic model was time consuming, the ERG only estimated deterministic pairwise ICERs.

3.33 The ERG considered that the resource-use for neurology visits in the manufacturer's economic model was 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 (£205) because the manufacturer assumed that the cost of a neurology visit was equal to the cost of a day-case admission (£590). The ERG also used alternative estimates for the inclusion of annual MRI scans for patients taking natalizumab and the inclusion of nurse visits for patients taking injectable treatments. Using these alternative monitoring resource assumptions, the ERG estimated that its base-case ICER increased from £21,414 to between £21,419 and £28,973 per QALY gained for dimethyl fumarate compared with Rebif-22.

3.34 The ERG explored alternative assumptions around the rates of stopping treatment. Changing the rates of stopping treatment to 50% of the original relative risks of stopping treatment estimated in the mixed treatment comparison after 2 years and to 0% after 2 years of treatment increased the ERG's estimated base-case ICER for dimethyl fumarate compared with Rebif-22 from £21,414 to £23,278 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 initial treatment in the manufacturer's economic model they receive placebo or 'best supportive care', and then progress more quickly through the EDSS

states. Switching from treatment to no treatment reduces costs to a greater extent than it reduces QALYs; if more patients stop treatment, the treatment becomes more cost effective. The ERG raised the concern that if best supportive care were specified in the scope as one of the comparators, the ICER for dimethyl fumarate compared with an active treatment would never be lower than the ICER for dimethyl fumarate compared with best supportive care. However, the ERG considered that in clinical practice patients who stop treatment because of adverse reactions will take another active treatment if an alternative (with a differing side-effect profile) is available.

- 3.35 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 into its exploratory analyses utility values from 2 other sources based on the UK Multiple Sclerosis Survey. These sources were the utility values reported in [Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis](#) (NICE technology appraisal guidance 127), and 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 about the utility values in all sources because the differences between secondary progressive multiple sclerosis and relapsing-remitting multiple sclerosis, and between relapse and 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 £18,700 and £22,144 per QALY gained when using the utility values from Orme et al. (2007) and NICE technology appraisal guidance 127 respectively.
- 3.36 The ERG considered that using different EDSS state costs for people with relapsing-remitting multiple sclerosis and people with secondary

progressive multiple sclerosis is appropriate. It was aware of 3 sources reporting costs by EDSS state 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 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 £2028 to be too high after receiving advice from clinicians that only 20% of relapses need hospitalisation. When the ERG varied the cost per relapse to between £3039 and £280 the ICER changed from £21,414 to between £18,660 and £26,074 per QALY gained respectively, for dimethyl fumarate compared with Rebif-22.

- 3.37 Although the manufacturer 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 estimating 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 disutility values for influenza and flu-like symptoms because the manufacturer's estimate seemed unreasonably high. Updating these disutility values had very little impact on the ICERs.

Manufacturer's additional evidence

- 3.38 The manufacturer provided additional evidence in its response to consultation. The manufacturer presented the results of the outcomes of relapse and of disability progression adjusted only for baseline relapse rate from the DEFINE and CONFIRM trials. These results were similar to

the analyses presented in its original submission adjusted for age, EDSS score, baseline relapse rate and geographical region (see sections 3.4 to 3.5). The manufacturer's revised mixed treatment comparison adjusted for baseline relapse rate estimated similar treatment effects relative to placebo to those originally presented in its unadjusted analysis (see sections 3.10 to 3.11). The manufacturer stated that its original mixed treatment comparison unadjusted for covariates (although the individual trial data within the mixed treatment comparison may have been adjusted for baseline rate) was more appropriate than the mixed treatment comparison adjusted for baseline relapse rate because the statistics describing model fit performed better and the unadjusted results more closely reflected the individual trial results. The results from the trials and mixed treatment comparison adjusted for baseline relapse rate are marked as academic in confidence by the manufacturer and cannot be presented here.

- 3.39 The manufacturer presented interim data from its ongoing open-label ENDORSE extension study of dimethyl fumarate (n=1736). The manufacturer stated that the efficacy outcomes suggest dimethyl fumarate's treatment effect is maintained at 4 years (annualised relapse rate: 0.142, 95% CI 0.108 to 0.187; proportion relapsed: 36.2%, 95% CI 32.1% to 40.6%; proportion with confirmed disability progression sustained over 24 weeks: 15.4%, 95% CI 12.4% to 18.9%). The manufacturer also noted that the safety data showed no new or worsening safety outcomes.
- 3.40 The manufacturer presented clinical-effectiveness data for highly active relapsing-remitting multiple sclerosis that were not available at the time of original submission. The manufacturer commented that the patient numbers in each treatment group were small in the analysis of the highly active relapsing-remitting multiple sclerosis subgroup, but the results were consistent with the results for the overall relapsing-remitting multiple sclerosis population. In a pooled analysis of the DEFINE and CONFIRM trials, high disease activity was defined as:
- an unchanged or increased relapse rate compared with the previous year despite treatment with beta interferon
 - at least 1 relapse in the previous year while on beta interferon therapy, and at

least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion.

In the pooled analysis of patients with high disease activity, the annualised relapse rate at 2 years was 0.20 with dimethyl fumarate and 0.36 with placebo (rate ratio 0.57, 95% CI 0.39 to 0.84). In the pooled analysis of patients with high disease activity, the proportion of patients with disability progression sustained for 3 months at 2 years was 0.18 with dimethyl fumarate and 0.16 with placebo (HR 1.19, 95% CI 0.66 to 2.15). The manufacturer did not submit a mixed treatment comparison or cost-effectiveness estimates for people with highly active relapsing-remitting multiple sclerosis.

3.41 The manufacturer provided revised cost-effectiveness analyses as part of the additional evidence. The manufacturer presented probabilistic pairwise ICERs and fully incremental analyses for dimethyl fumarate compared with each of the comparators, incorporating the following data requested by the Appraisal Committee:

- the results of the mixed treatment comparison adjusted for baseline relapse rate for the outcomes 'annualised relapse rate' and 'disability progression sustained for 3 months at 2 years'
- a reduced cost of relapse (but the manufacturer chose to reduce the cost of relapse from £2028 in its original submission to £1206 in its revised analysis rather than £607.80, as preferred by the Committee at its first meeting)
- the number and cost of neurology visits, as preferred by the ERG in its exploratory analyses
- a sensitivity analysis including non-medical costs.

3.42 In the manufacturer's probabilistic pairwise analysis excluding non-medical costs in the active relapsing-remitting multiple sclerosis population, dimethyl fumarate:

- dominated fingolimod and Betaferon
- compared with glatiramer acetate, resulted in incremental costs of £8481 and incremental QALYs gained of 0.22, with an ICER of £37,897 per QALY gained
- compared with Rebif-22, resulted in incremental costs of £7902 and

incremental QALYs gained of 0.23, with an ICER of £34,819 per QALY gained

- compared with Rebif-44, resulted in incremental costs of £3831 and incremental QALYs gained of 0.13, with an ICER of £29,502 per QALY gained
- compared with Avonex, resulted in incremental costs of £1380 and incremental QALYs gained of 0.16, with an ICER of £8818 per QALY gained
- compared with natalizumab, resulted in incremental cost savings of £46,264 and an incremental QALY loss of 0.08.

In fully incremental analyses, glatiramer acetate was the least costly treatment in the scenario that excluded non-medical costs followed by Rebif-22, Rebif-44, Avonex, dimethyl fumarate, Betaferon, fingolimod and natalizumab. Glatiramer acetate dominated Rebif-22 and Rebif-44 dominated Avonex. Rebif-44 was extendedly dominated (that is, a combination of 2 or more treatments provided the same health gain as Rebif-44, but at a reduced cost). Therefore the ICER for dimethyl fumarate in the fully incremental analysis excluding non-medical costs was based on a comparison with glatiramer acetate with an estimated ICER of £37,897 per QALY gained. In the sensitivity analysis including non-medical costs, glatiramer acetate remained the reference comparator for dimethyl fumarate, with an estimated probabilistic ICER of £39,363 per QALY gained.

3.43 The manufacturer also presented pairwise ICERs, as well as a fully incremental analysis, for a scenario using its own preferred assumptions. These included:

- the results of the unadjusted (rather than adjusted) mixed treatment comparison
- its original assumptions for the number of visits to a neurologist beyond year 2 needed by patients taking dimethyl fumarate based on the summary of product characteristics (that is, 1 visit per year rather than the ERG's suggested 2 visits per year)
- a reduced cost of relapse (the manufacturer considered that using the reduced cost of relapse of £607.80 as requested in the appraisal consultation document was too conservative, and therefore chose to use a reduced cost of relapse of £1206 based on estimates from 1 of its internal surveys of 15 multiple sclerosis

consultants).

3.44 In the manufacturer's probabilistic pairwise analysis for the active relapsing-remitting multiple sclerosis population that excluded non-medical costs, but which incorporated its own preferred assumptions, dimethyl fumarate:

- dominated fingolimod and Betaferon
- compared with glatiramer acetate, resulted in incremental costs of £7209 and incremental QALYs gained of 0.26, with an ICER of £27,692 per QALY gained
- compared with Rebif-22, resulted in incremental costs of £7103 and incremental QALYs gained of 0.23, with an ICER of £30,986 per QALY gained
- compared with Rebif-44, resulted in incremental costs of £3018 and incremental QALYs gained of 0.13, with an ICER of £22,748 per QALY gained
- compared with Avonex, resulted in incremental costs of £650 and incremental QALYs gained of 0.16, with an ICER of £3994 per QALY gained
- compared with natalizumab, resulted in incremental cost savings of £47,198 and an incremental QALY loss of 0.08.

In the manufacturer's fully incremental probabilistic analyses for the scenario using its preferred assumptions and excluding non-medical costs, glatiramer acetate was the least costly treatment in the analysis followed by Rebif-22, Rebif-44, Avonex, dimethyl fumarate, Betaferon, fingolimod and natalizumab. Avonex was dominated by Rebif-44 and Rebif-44 was extendedly dominated. The ICER for dimethyl fumarate in this fully incremental analysis was based on a comparison with Rebif-22 with an estimated ICER of £30,986 per QALY gained. In the sensitivity analysis including non-medical costs, Rebif-22 remained the reference comparator for dimethyl fumarate with an estimated ICER of £31,224 per QALY gained. The manufacturer provided additional analyses relating to the sequence of treatments. The manufacturer presented scenarios exploring the probabilistic cost-effectiveness estimates for 8 treatment sequences. In all sequences, dimethyl fumarate replaced a treatment (for example, dimethyl fumarate, Avonex and glatiramer acetate compared with Rebif-44, Avonex and glatiramer acetate). In 6 of the 8 scenarios, dimethyl fumarate was included as first-line treatment, in 2 as

second-line treatment. For 4 of the 8 scenarios presented, the sequences that included dimethyl fumarate dominated the comparator sequences without dimethyl fumarate. The other 4 scenarios resulted in probabilistic ICERs ranging between £5083 and £36,491 per QALY gained for the treatment sequence including dimethyl fumarate compared with the sequence including a comparator.

3.45 In response to the request in the appraisal consultation document for external validation of its economic model, the manufacturer presented cost-effectiveness results for all of the beta interferons and for glatiramer acetate compared with no treatment. The aim of the validation was to determine how similar the ICERs from the manufacturer's economic model were to those in the NHS risk-sharing scheme for multiple sclerosis. To more closely reflect the structural assumptions of the NHS risk-sharing scheme economic model, the manufacturer adapted its economic model to include a 20-year time horizon and excluded the possibility that the effectiveness of treatments wanes over time. The manufacturer's deterministic ICERs compared with no treatment were as follows:

- Avonex: £64,866 per QALY gained
- Betaferon: £145,029 per QALY gained
- glatiramer acetate: £72,731 per QALY gained
- Rebif-22: £66,057 per QALY gained
- Rebif-44: £53,383 per QALY gained.

The manufacturer stated that its deterministic ICERs were similar to the NHS risk-sharing scheme (deterministic) ICERs. However, it concluded that the ICERs from its economic model and from the NHS risk-sharing scheme were not directly comparable because health economic methodology and the NICE 'reference case' have changed since 2002.

ERG comments on the manufacturer's additional evidence

- 3.46 The ERG reviewed the additional evidence presented by the manufacturer and commented that it appropriately addressed the analyses requested in the appraisal consultation document. The ERG noted that adjusting the trial outcomes for baseline relapse rate made little difference to the values reflecting disability progression and relapse. The ERG stated that using the results of the manufacturer's unadjusted mixed treatment comparison was reasonable because there were too few studies in the network to estimate the effect of a covariate with precision.
- 3.47 The ERG noted that the manufacturer's probabilistic ICERs, which excluded non-medical costs, were similar to those including non-medical costs. The ERG commented that the manufacturer did not explain how it estimated the costs of each EDSS state when including or excluding non-medical costs. For some EDSS states, the manufacturer estimated higher costs when excluding non-medical costs than when including non-medical costs. However, the ERG noted that these differences were small. The ERG stated that the cost of relapse (£1206) chosen by the manufacturer may be plausible but the lower cost of relapse requested in the appraisal consultation document (£607.80) also remains plausible. The ERG explored a scenario that used £607.80, which led to only a small increase in the ICERs for dimethyl fumarate compared with each treatment. The ERG considered its 'alternative' assumption for the number of neurology visits (2 visits instead of 1) in year 2 onwards, which it had been informed by a clinical adviser was plausible.
- 3.48 The ERG noted that treatment sequences starting with dimethyl fumarate estimate higher ICERs than sequences that start with either glatiramer acetate or Rebif. It also highlighted that a limitation of the analysis is that the effectiveness of the treatments is assumed to be the same no matter the position in the treatment pathway, but that this could be a constraint of the available data.
- 3.49 The ERG commented that, when the manufacturer externally validated its model, it estimated results that differed from those estimated in the NHS

risk-sharing scheme (see section 3.45). Given the information available, the ERG could not explore the reasons for these differences. The ERG acknowledged that health economic methods have evolved since the publication of the ICERs associated with the NHS risk-sharing scheme, including, for example, the use of mixed treatment comparisons, changes in discount rates used for costs and health effects, and the use of probabilistic analyses.

3.50 Full details of all the evidence are in the [evaluation report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dimethyl fumarate, having considered evidence on the nature of relapsing-remitting multiple sclerosis and the value placed on the benefits of dimethyl fumarate by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee heard from the clinical specialists and patient experts about the nature of the condition. It heard that relapsing-remitting multiple sclerosis is a chronic, disabling, neurological condition that often has a substantial negative impact on quality of life and activities of daily living. The patient experts emphasised that as the disease progresses patients can lose independence and the capacity for employment. The Committee heard from the patient experts that only 25% of patients with multiple sclerosis are in employment compared with 75% of the general population who are of working age, and that 80% of people who have had multiple sclerosis for 15 years or more are not working. The patient experts emphasised the importance of having access to new treatments that could reduce the number of relapses and delay disability. The Committee noted that the current first-line treatments for relapsing-remitting multiple sclerosis need to be injected and can be associated with unpleasant side effects (such as injection-site reactions or flu-like symptoms, fatigue and depression) and can significantly affect patients' emotional wellbeing. The Committee heard from the patient experts that because dimethyl fumarate is taken orally, it would allow more flexibility and decrease discomfort compared with injectable treatments. The Committee heard further from the patient experts that people with relapsing-remitting multiple sclerosis may need to take corticosteroids, which in some instances are administered intravenously over several days, and considered that the anti-inflammatory effect of dimethyl fumarate could reduce the need for corticosteroids. The Committee understood that any delay in relapse and progression of disability, or relief from using injectable treatments and corticosteroids, would have a positive impact on the lives of people with multiple sclerosis and their families.

- 4.3 The Committee discussed the management of relapsing-remitting multiple sclerosis and considered the likely position of dimethyl fumarate in the treatment pathway for adults with this condition. The Committee heard from the clinical specialists that, as recommended in the Association of British Neurologists' guidelines, most patients who have had 2 relapses in the previous 2 years would be offered a disease-modifying therapy (one of the beta interferons [Avonex, Rebif, Betaferon or Extavia] or glatiramer acetate) and enrolled in the risk-sharing scheme that has been agreed between the Department of Health and the manufacturers. The Committee understood that the risk-sharing scheme was established by the Department of Health in 2002 after beta interferons and glatiramer acetate were considered not to be cost effective ([Beta interferon and glatiramer acetate for the treatment of multiple sclerosis](#) NICE technology appraisal guidance 32). As a result, the financial risk is shared between the NHS and the participating pharmaceutical companies.
- 4.4 The Committee heard from the clinical specialists that the treatments prescribed in clinical practice in the UK vary because there is no single treatment pathway. The clinical specialists explained that clinicians and patients together choose a disease-modifying therapy taking into account lifestyle, the route and schedule of administration, the side-effect profile, and how the drug is stored. The clinical specialists explained that because it was a personal choice, there was no preferred first-line treatment. However the clinical specialists stated there would be circumstances when a drug is not prescribed; for instance, beta interferon would be avoided in a patient with, or at risk of, depression. The Committee also heard from the clinical specialists that patients would be offered a different disease-modifying therapy if they experienced more frequent relapses, there was evidence of increased disease activity on MRI, or they had adverse reactions to the treatment. The Committee heard from the clinical specialists that dimethyl fumarate would be considered as a treatment option in the same way as beta interferons or glatiramer acetate in people with relapsing-remitting multiple sclerosis eligible for active treatment under the Association of British Neurologists' guidelines. The clinical specialists also considered that dimethyl fumarate may provide a treatment option for people with relapsing-remitting multiple sclerosis previously treated with beta

interferons or glatiramer acetate whose disease had failed to respond or who had experienced adverse reactions. The Committee understood from the clinical specialists that the use of disease-modifying therapies decreases as a patient's Expanded Disability Status Scale (EDSS) score increases and stopping treatment is determined by the accumulation of disability (reaching EDSS 7) or by the development of secondary progressive multiple sclerosis.

- 4.5 The Committee discussed the management of rapidly evolving severe relapsing-remitting multiple sclerosis and highly active relapsing-remitting multiple sclerosis. The Committee heard from the clinical specialists that more aggressive disease, that is, rapidly evolving severe, or highly active relapsing-remitting multiple sclerosis, may be difficult to diagnose early in the course of the disease, but if the prescribing clinician was confident that a patient had aggressive disease, then the clinician would offer the patient natalizumab or fingolimod rather than dimethyl fumarate. The Committee was aware that if a patient had received beta interferon as a first-line therapy, NICE recommends fingolimod as an option for the treatment of highly active relapsing-remitting multiple sclerosis in adults who, compared with the previous year, have an unchanged or increased relapse rate or ongoing severe relapses ([Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis](#) NICE technology appraisal guidance 254). The Committee was also aware that NICE recommends natalizumab for the treatment of people with rapidly evolving severe relapsing-remitting multiple sclerosis ([Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis](#) NICE technology appraisal guidance 127). Although dimethyl fumarate would not be offered to patients with rapidly evolving severe relapsing-remitting multiple sclerosis, the clinical specialists noted that because natalizumab is associated with progressive multifocal leukoencephalopathy, dimethyl fumarate could be considered as a first-line treatment option in people with rapidly evolving severe relapsing-remitting multiple sclerosis who are at a high risk of developing progressive multifocal leukoencephalopathy (such as those who test positive for John Cunningham virus).

Clinical effectiveness

4.6 The Committee discussed the clinical-effectiveness evidence from the DEFINE and CONFIRM trials. It heard from the clinical specialists that the trial populations broadly represent patients who would be offered beta interferon or glatiramer acetate in the UK, in line with the Association of British Neurologists' guidelines. The Committee noted that the trial populations had more severe relapsing-remitting multiple sclerosis than the population covered by the marketing authorisation. The Committee noted that the 2 trials included different primary endpoints for measuring relapse, that is, the proportion of patients with relapse at 2 years in the DEFINE trial and the annualised relapse rate in the CONFIRM trial, and heard from the manufacturer that this was because the European Medicines Agency and the Food and Drug Administration preferred different approaches to measuring relapse. The Committee heard from the clinical specialists that the 2 endpoints have the same influence on clinical decisions. In addition, the Committee heard from the clinical specialists and patient experts that it is difficult to define a relapse because each relapse varies in nature and severity, and that it is the disability that follows, rather than the relapse itself, that has the greater impact on the patient's health-related quality-of-life. The Committee acknowledged that confirming a relapse may include a degree of subjectivity. The Committee noted that the results presented from the manufacturer's trials and meta-analysis showed that dimethyl fumarate statistically significantly reduced both the rate of relapses and the proportion of patients experiencing a relapse compared with placebo. The Committee discussed the manufacturer's approaches to analysing the efficacy outcomes for its trials. The Committee was concerned about a few aspects of the analysis: in its original submission, the manufacturer had adjusted the analysis for a number of factors, including region. However, the manufacturer clarified that the statistical analyses of data by region had been documented in the statistical analysis plan prior to data base lock and as such had constituted a pre-specified analysis. The Committee also noted that patients in the DEFINE and CONFIRM trials taking dimethyl fumarate experienced more flushing than patients taking placebo and this may have led to functional unblinding of the treatment arms. However, the ERG confirmed that protocols were put in place to avoid functional unblinding. The Committee concluded that, overall, the

evidence suggested that dimethyl fumarate reduces relapses in people with relapsing-remitting multiple sclerosis compared with placebo.

- 4.7 The Committee was aware of another factor potentially affecting the magnitude of the treatment effect of dimethyl fumarate compared with placebo, in that patients in the DEFINE and CONFIRM trials were eligible to switch to alternative active therapies for multiple sclerosis if they had 1 or more relapse or confirmed progression of disability for 3 months. The Committee acknowledged that a higher proportion of patients randomised to placebo (13%) switched to active treatment than patients randomised to dimethyl fumarate (6%). The Committee heard from the manufacturer that in its base-case efficacy analysis, it included only outcomes measured before patients switched treatment, but conducted a sensitivity analysis that included outcomes after patients switched treatment. However, the estimated treatment effect for dimethyl fumarate compared with placebo did not differ between the base-case analysis and this sensitivity analysis. The Committee concluded that it was satisfied that switching to alternative treatments in the DEFINE and CONFIRM trials did not affect the estimated treatment effect of dimethyl fumarate compared with placebo as measured by the primary efficacy end points.
- 4.8 The Committee discussed the results of the manufacturer's mixed treatment comparison for disability progression. It understood that in response to clarification requests from the Evidence Review Group (ERG), the manufacturer revised its estimates for the sustained disability progression outcomes, presenting the effect measure as hazard ratios rather than risk ratios as in its original submission. The Committee heard from the ERG that it preferred hazard ratios because they represent the instantaneous risk over the study period whereas risk ratios measure the cumulative risk over the entire study. The Committee concluded that it was more appropriate to measure outcomes measuring sustained disability progression using hazard ratios.
- 4.9 The Committee discussed the trials' outcome measure of sustained disability progression. The Committee noted that the manufacturer's mixed treatment comparison suggested that compared with placebo, dimethyl fumarate statistically significantly reduced confirmed disability

progression sustained for 3 months in the 2 years of the trials, but the reduction for disability progression sustained for 6 months at 2 years was not statistically significant. The Committee heard from the clinical specialists that patients may not have permanent disability progression after a relapse and that recovery may take up to 12 months, but on average people will recover within 3 or 4 months. The clinical specialists stated that sustained disability progression lasting for 6 months is a more appropriate outcome measure than disability progression lasting for 3 months, and it was also preferred by the European Medicines Agency in its draft guideline for the clinical investigation of medicinal products for the treatment of multiple sclerosis. The Committee heard from the ERG that most trials of relapsing-remitting multiple sclerosis measure sustained disability progression lasting for 3 months, and the Committee agreed that it would consider this in its decision-making. However, the Committee concluded that sustained disability progression confirmed for 6 months provides a more robust indication of the treatment effect given that patients may recover from relapse.

- 4.10 The Committee was aware that the diagnostic criteria, clinical management and prognosis of multiple sclerosis have changed since the year 2000. The Committee noted that the manufacturer included trials that were published before the year 2000 in its mixed treatment comparison, and that the ERG observed differences among the baseline relapse rates of the trials of relapsing-remitting multiple sclerosis. The Committee heard from the ERG that these differences were likely to be clinically meaningful, in that there is potential for more heterogeneity when using an unadjusted model (rather than a model adjusted for baseline relapse as a covariate). The Committee understood that, in response to consultation, the manufacturer had presented additional analyses of relapse rate and disability progression from its trials and the mixed treatment comparison adjusted for baseline relapse rate only. The Committee noted that adjusting the trial outcomes only for baseline relapse rate (rather than for baseline age, EDSS, relapse rate and geographical region) and the mixed treatment comparison only for baseline relapse rate (rather than unadjusted) did not change the results. The Committee questioned why the statistics reflecting model fit performed better for the unadjusted model than for the adjusted model. The Committee heard from the manufacturer that it had not tested either

the adjusted or unadjusted mixed treatment comparison for heterogeneity. The Committee considered that estimating heterogeneity for each approach would better indicate the most appropriate approach. The Committee concluded that there remains some uncertainty about whether the manufacturer had appropriately modelled the adjustment for baseline relapse rate in its mixed treatment comparison, but that in this case it preferred the results of the unadjusted mixed treatment comparison because it provided the better statistical fit.

- 4.11 The Committee discussed the results of the mixed treatment comparisons and agreed that they showed that dimethyl fumarate is more effective than beta interferons and glatiramer acetate in reducing relapses. However, a treatment effect on disability progression was less clear in that the hazard ratios for disability progression indicated an effect of dimethyl fumarate compared with beta interferons and glatiramer acetate but the difference was not statistically significant. The Committee concluded that, compared with beta interferons and glatiramer acetate, dimethyl fumarate is more effective in reducing relapse rates and as effective for disability progression.
- 4.12 The Committee noted that, in response to consultation, the manufacturer presented evidence of clinical effectiveness for dimethyl fumarate compared with placebo for the highly active relapsing-remitting multiple sclerosis subgroup from its DEFINE and CONFIRM trials. The Committee commented that the number of patients with highly active relapsing-remitting multiple sclerosis in the trials was low, and that the data suggested that dimethyl fumarate was beneficial in terms of reducing relapses (with a statistically significant rate ratio according to the confidence interval). The treatment effect on disability progression was less clear because of the small sample size (with a hazard ratio suggesting that dimethyl fumarate increased the hazard of disability progression, but with no statistical significance according to the confidence interval). The Committee also noted that no trials exist that directly compare dimethyl fumarate with either fingolimod or natalizumab, and that the manufacturer had not submitted a mixed treatment comparison for patients with highly active relapsing-remitting multiple sclerosis or with rapidly evolving severe relapsing-remitting multiple sclerosis respectively. Therefore, the Committee agreed that it

could not draw any conclusions about the clinical effectiveness of dimethyl fumarate compared with natalizumab or with fingolimod in the respective subgroups. The Committee concluded that it had insufficient evidence from the manufacturer to recommend dimethyl fumarate in these subgroups.

- 4.13 The Committee considered the safety data from the DEFINE and CONFIRM trials, which showed that patients taking dimethyl fumarate experienced more gastrointestinal events and flushing and skin reactions, particularly in the first months of treatment, than patients not taking dimethyl fumarate. The Committee heard from the manufacturer that most of these episodes were mild to moderate in severity and that approximately 4% of patients taking dimethyl fumarate discontinued the study drug because of flushing. It was also aware that episodes of progressive multifocal leukoencephalopathy reported in patients taking Fumaderm or a compound formulation of dimethyl fumarate and copper monomethyl fumarate are unlikely to be relevant here, and that no episodes of progressive multifocal leukoencephalopathy had been reported in patients taking dimethyl fumarate. The Committee concluded that, although dimethyl fumarate can lead to several different adverse reactions, it is generally well tolerated.

Cost effectiveness

- 4.14 The Committee commented that the manufacturer had submitted a model structurally similarly to models used in previous NICE technology appraisals. The Committee concluded that it could consider only the ICERs for dimethyl fumarate compared with beta interferons and glatiramer acetate because of the lack of data for the subgroups for whom natalizumab and fingolimod have been recommended (see section 4.12).
- 4.15 The Committee discussed how the manufacturer modelled the natural history of multiple sclerosis. It commented that it was appropriate to allow modelled patients with relapsing-remitting multiple sclerosis to move to lower as well as to higher EDSS states, that is, to allow for the condition to improve and to get worse, which is in line with what is seen in clinical practice for patients in the lower EDSS states. The Committee

noted the inherent limitations associated with using the London Ontario dataset to model the natural history of disease, namely, that it allowed only for movement to higher EDSS states, and that it reflected a patient population from the 1970s and 1980s. However, the Committee understood that the manufacturer had used the London Ontario data set to model the natural history of disease only for EDSS scores of 7 or more in patients with relapsing-remitting multiple sclerosis, for rates of progression to secondary progressive multiple sclerosis, and in patients with secondary progressive multiple sclerosis. The Committee also heard from the clinical specialists that once patients are in a higher EDSS state they are less likely to relapse, and therefore the possibility of moving to lower EDSS states is less plausible. The Committee recognised that the manufacturer had used the DEFINE and CONFIRM trial data to model the natural history of relapsing-remitting multiple sclerosis at lower EDSS states, that the model allowed patients to move to lower EDSS states, and that the trial population more closely reflected the population in UK clinical practice than did the population in the older London Ontario data set, especially considering that the prognosis for people with multiple sclerosis has improved in the last 20 years. The Committee concluded that by using its trial data, the manufacturer had appropriately modelled the natural history of disease.

- 4.16 The Committee discussed the mortality data included in the manufacturer's economic model. It was aware that the manufacturer had used mortality multipliers by EDSS score from Pokorski et al. (1997) in a Danish population diagnosed with multiple sclerosis from 1948 onwards. The Committee heard from the clinical specialists that they would anticipate that the relative risk of mortality in people with multiple sclerosis compared with the general population is lower than reported in this publication because the life expectancy of people with multiple sclerosis has improved. However, the Committee was aware that the manufacturer provided scenario analyses around mortality that showed that this had little impact on the ICERs and therefore concluded that it did not need to pursue this issue any further.
- 4.17 The Committee noted that because the trials lasted 2 years, but the manufacturer assumed that patients would take dimethyl fumarate indefinitely, the manufacturer modelled a waning of treatment effect

because of the uncertain longer-term benefits of dimethyl fumarate. The Committee heard from the clinical specialists that the manufacturer's assumption seemed reasonable but, given the uncertainty, they could not comment on the degree to which dimethyl fumarate's effect might wane. The Committee also recognised that it may be possible that the effect of dimethyl fumarate might wane at a different rate than other treatments, but this was uncertain. Therefore, the Committee accepted the manufacturer's approach using the same rate of waning of effect for each treatment. The Committee noted that, in response to consultation, the manufacturer presented data from the open-label ENDORSE extension study, which suggested that dimethyl fumarate maintains its effect over 4 years. The Committee noted that the treatment effect in the economic model waned to 75% after 2 years, and therefore the manufacturer's model may have overestimated waning in the short term. However, the Committee recognised that the manufacturer had used a time horizon of 30 years in its economic model and therefore the longer-term benefits of the treatment remained unknown. The Committee concluded that a cautious modelling approach was appropriate.

- 4.18 The Committee discussed the costs and resource use values included in the manufacturer's economic model. The Committee heard from the ERG that several publications were available that presented the annual costs of relapsing-remitting multiple sclerosis by EDSS state, and that although they were also based on the UK Multiple Sclerosis Survey, the annual costs by EDSS state varied considerably. The ERG explained to the Committee that each publication used different unit costs and different cost items, and that some of the cost items were non-medical (and therefore potentially not considered from the perspective of the NHS and personal social services), and so it was unclear whether these items met the NICE reference case, as detailed in NICE's [Guide to the methods of technology appraisal](#)). The Committee understood from the ERG that it was unable to judge the most appropriate data source for annual costs by EDSS state, and that an approach that removed non-medical costs was more plausible (unless the manufacturer could prove that the non-medical costs met the NICE reference case). The Committee was aware that, in response to consultation, the manufacturer explored the impact of including or excluding all non-medical costs because it was not

possible to identify in the data set the non-medical costs relating to personal social services relevant to the NICE reference case. The Committee heard from the ERG that, for some EDSS states, the manufacturer had estimated higher costs when excluding rather than including non-medical costs. However, the Committee noted that using either approach in the manufacturer's economic model had little impact on the ICERs. The Committee concluded that it preferred excluding non-medical costs, but acknowledged that the ICERs were likely to be lower for dimethyl fumarate if the personal social services costs had been included.

- 4.19 The Committee was also aware that the manufacturer's chosen number and cost of visits to a neurologist needed by patients differed from those preferred by the ERG. The Committee considered that the number of visits included in the manufacturer's model was reasonable because patients taking dimethyl fumarate were unlikely to need more intensive monitoring than patients using other disease-modifying treatments. However, the Committee agreed that the ERG's assumed cost (outpatient) for a visit to a neurologist was more plausible than the manufacturer's (day case). The Committee noted that the manufacturer had lowered the cost of relapse in its revised model in response to consultation, but not to the value preferred by the Committee ([section 3.41](#)). However, it heard from the ERG that either of these 2 lower values could be plausible and had little impact on the ICERs. The Committee was disappointed that all of the sources used by the manufacturer to estimate the cost of relapse were of low methodological quality, and encouraged further research to identify more robust data for future NICE technology appraisals. The Committee was satisfied that, given the current evidence, the manufacturer adequately addressed and explored all of the uncertainties associated with the costs in the economic model.
- 4.20 The Committee noted that the manufacturer had collected EQ-5D utility data in its clinical trials of dimethyl fumarate for people with relapsing-remitting multiple sclerosis without relapses, and adjusted these values for patients with secondary progressive multiple sclerosis and for patients experiencing a relapse using data from the UK Multiple Sclerosis Survey (see [section 3.18](#)). The Committee heard from the

clinical specialists that the health-related quality-of-life of people with multiple sclerosis was more closely related to their EDSS score than to the clinical form of their multiple sclerosis (that is, relapsing-remitting or secondary progressive). The clinical specialists stated that it is difficult to clearly identify when a patient's disease becomes secondary progressive multiple sclerosis, and therefore it is also difficult to gauge the relative health-related quality-of-life effects of the different clinical forms of multiple sclerosis. The Committee acknowledged that the ERG's exploratory analyses showed that using alternative utility values and alternative assumptions relating to the rate of conversion from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis had little impact on the ICERs. The Committee noted that the model included disutility to carers of people with relapsing-remitting multiple sclerosis that increased with increasing disability of the patient. The Committee was aware that carer disutility had featured in [Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis](#) (NICE technology appraisal guidance 254) and [Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis](#) (NICE technology appraisal guidance 127), and concluded that including these carer disutility values was appropriate. It noted that the ERG updated the disutility of flu-like symptoms and flu in its exploratory analyses of the manufacturer's economic model but this had little impact on the estimated ICERs. The Committee concluded that the results of the ICERs were robust to changes in these parameters, and considered that the EQ-5D utility values from the trial represented the best evidence available because they more closely reflected the population with relapsing-remitting multiple sclerosis treated with disease-modifying therapy in UK clinical practice.

- 4.21 The Committee discussed the assumption in the manufacturer's original economic model that people with relapsing-remitting multiple sclerosis do not switch to another active treatment when their disease does not respond, or when they have adverse reactions. The Committee recognised that, whereas no specific sequence of disease-modifying treatments defines standard practice in the NHS, it heard from the clinical specialists that people with relapsing-remitting multiple sclerosis are likely to take another treatment in these circumstances, and confirmed that people would choose a treatment with a different

side-effect profile. The Committee noted that, in response to consultation, the manufacturer had provided cost-effectiveness estimates for dimethyl fumarate when included in a treatment sequence. The Committee heard from the ERG that, when dimethyl fumarate is included in a treatment sequence, the resulting ICERs were slightly higher than those estimated in the manufacturer's original model, which excluded subsequent treatments. The Committee considered it important to explore the sensitivity of the ICERs from different treatment sequences, and agreed that, for future NICE multiple technology appraisals in multiple sclerosis, exploring several sequences would be useful. However, the Committee concluded that analysing individual drugs (without a sequence) was appropriate for its decision-making in this appraisal because:

- there is no established common treatment pathway
- of uncertainties related to modelling sequences
- fully considering treatment sequences goes beyond the scope of this appraisal.

4.22 The Committee understood that the main drivers of the ICERs were the costs of treatment, how likely a patient was to experience disease progression, the probability of stopping treatment, and the magnitude of the treatment waning effect. The Committee heard from the clinical specialists that the rate of stopping treatment is likely to be lower in the longer term than that observed in the 2-year trials because patients are more likely to have adverse reactions and discontinue treatment early in the treatment course. The Committee noted the ERG's observation that in the manufacturer's economic model, the sooner a patient stops treatment, the more cost effective the treatment appears ([section 3.34](#)). The Committee noted that the manufacturer, in response to consultation, carried out an external validation exercise to explore how similar the cost-effectiveness estimates for current active treatments (all beta interferons and glatiramer acetate) compared with no treatment in its model were to those already established for the NHS risk-sharing scheme for multiple sclerosis. It acknowledged that the manufacturer attempted to update its economic model to reflect the model used in the NHS risk-sharing scheme as closely as possible, but noted that some differences remained between the models (for example, between the

sources of evidences used, methods used to synthesise the evidence and structural assumptions). The Committee noted that the manufacturer and ERG were unable to explain any differences between the ICERs resulting from the manufacturer's model and from the model behind the risk-sharing scheme, and highlighted that there was still uncertainty related to the validity of the manufacturer's model. The Committee acknowledged that showing close convergence between the previous and present analyses was challenging. The Committee concluded that it was satisfied that the manufacturer's economic model was sufficiently robust for decision-making.

4.23 The Committee noted that the manufacturer's revised ICERs estimated from deterministic analyses were substantially lower than the ICERs estimated from probabilistic analyses. It heard from the manufacturer that this is because it included uncertainty around EDSS state transitions for which there is no evidence because they were not observed in the trial (for example, moving from the lower EDSS states of relapsing-remitting multiple sclerosis to the higher EDSS states of relapsing-remitting multiple sclerosis, such as from EDSS 1 to EDSS 6, 7, 8 or 9). The manufacturer highlighted to the Committee that it considered the probabilistic ICERs to be conservative estimates of cost effectiveness because the probabilistic ICERs were similar to the deterministic ICERs when the model did not include the uncertainty around the state transitions for which there was no evidence. The Committee considered it was appropriate to capture this uncertainty in the probabilistic analysis because some patients do experience these rare changes. The Committee was aware that the ERG also preferred probabilistic sensitivity analyses because of the non-linear nature of the manufacturer's economic model (see section 3.31). The Committee concluded that it preferred the probabilistic ICERs.

4.24 The Committee discussed the innovative nature of dimethyl fumarate and whether the economic analysis had captured all changes in health-related quality-of-life. In its submission, the manufacturer stated that dimethyl fumarate was innovative because it is taken orally, and because its mechanism of action targets the nuclear factor erythroid-derived 2-like 2 (Nrf2) pathway. The Committee recognised that a drug taken orally may give people with relapsing-remitting multiple

sclerosis a valuable alternative to current first-line treatment options, but acknowledged comments from professional and patient groups that its twice-daily administration schedule may lower adherence compared with once-daily options. The benefit related to being an oral drug was not captured in the analysis because the manufacturer's economic model applied the same utility values to dimethyl fumarate as to beta interferons and glatiramer acetate. The Committee therefore acknowledged that dimethyl fumarate provides health-related quality-of-life benefits other than those captured in the QALY calculation for patients currently taking beta interferons and glatiramer acetate, and that the ICER may decrease when the benefits of oral treatment were taken into consideration. The Committee heard from the clinical specialists that little is known about what causes multiple sclerosis and therefore it could not advise the Committee whether dimethyl fumarate's mechanism of action could be considered relevant to the pathophysiology of multiple sclerosis, and therefore innovative. The Committee also noted the comments received during consultation stating that dimethyl fumarate could be a preferred treatment option for women of child-bearing age because of its short washout period compared with another oral treatment currently available. The Committee concluded that dimethyl fumarate was innovative, and that additional health-related quality-of-life benefits associated with oral treatment and short washout duration may not have been fully captured within the manufacturer's economic modelling.

4.25 The Committee discussed the most plausible ICER for dimethyl fumarate for the group of people with relapsing-remitting multiple sclerosis whose disease is eligible for active treatment under the Association of British Neurologists' guidelines (see section 4.3). The Committee acknowledged that the manufacturer had used the best available evidence to model the natural history of the disease, used EQ-5D utility data as preferred by NICE in its [Guide to the methods of technology appraisal](#) and included waning of the treatment effect. The Committee agreed that the most plausible ICER should be based on:

- the unadjusted mixed treatment comparison
- the manufacturer's assumptions about monitoring

- the ERG's cost for a visit to a neurologist
- £1206 as a cost of relapse
- excluding non-medical costs (because the manufacturer was unable to identify those costs associated with personal social services that meet the NICE reference case).

The Committee noted that the total costs are relatively similar for dimethyl fumarate, beta interferons and glatiramer acetate, and observed that the reference comparator for dimethyl fumarate in a fully incremental analysis changes depending on the structure and data used in the economic model, as demonstrated by the external validation exercise. The Committee also acknowledged that, when compared with dimethyl fumarate, Rebif-22 appeared to be the most cost-effective comparator in the manufacturer's analysis, and that Rebif-22 is a 'step-down' therapy for patients who cannot tolerate the higher dosage (that is, Rebif-44). Therefore, the Committee disregarded the comparison of dimethyl fumarate with Rebif-22, and based the most plausible ICER on a comparison of dimethyl fumarate with glatiramer acetate (the next most cost-effective comparator after Rebif-22) using the manufacturer's preferred scenario, with an ICER of approximately £27,700 per QALY gained. It also agreed that the waning of effect in the short term (between 3 to 5 years) may have been modelled too high because 4-year data from ENDORSE suggest that the effect of treatment may not diminish up to that point. The Committee concluded that, if both this and the non-medical costs that are covered by the personal social services perspective are included in the analysis, the ICER of dimethyl fumarate would decrease. The Committee also noted that the benefits not captured in QALY gains, such as the oral administration of dimethyl fumarate and its shorter washout period, could also decrease the ICER. The Committee concluded that dimethyl fumarate could be considered a cost-effective use of NHS resources for treating relapsing-remitting multiple sclerosis in adults for whom beta interferons and glatiramer acetate would otherwise be considered as treatment options; that is, adults who have active relapsing-remitting multiple sclerosis, normally defined by 2 clinically significant relapses in the previous 2 years, but who do not have highly active relapsing-remitting multiple sclerosis or rapidly evolving severe relapsing-remitting multiple sclerosis, and only if the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.

Summary of Appraisal Committee's key conclusions

TA320	Appraisal title: Dimethyl fumarate for treating relapsing-remitting multiple sclerosis	Section
Key conclusion		
<p>Dimethyl fumarate is recommended as an option for treating adults with active relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if:</p> <ul style="list-style-type: none"> • they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis and • the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme. 		1.1
<p>The Committee concluded that, compared with beta interferons and glatiramer acetate, dimethyl fumarate is more effective in reducing relapse rates and as effective for disability progression.</p>		4.11
<p>The Committee concluded that it had insufficient evidence from the manufacturer to make recommendations for dimethyl fumarate in rapidly evolving severe, and highly active, relapsing-remitting multiple sclerosis.</p>		4.12
<p>The Committee concluded that, based on a comparison of dimethyl fumarate with glatiramer acetate, the most plausible ICER was likely to be below £27,700 per QALY gained, taking into consideration that waning of treatment effect may have been overestimated and also the benefits not captured in the economic modelling, such as the oral administration of dimethyl fumarate and its shorter washout period.</p>		4.25
Current practice		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee understood that any delay in relapse and progression of disability, or relief from using injectable treatments and corticosteroids, would have a positive impact on the lives of people with multiple sclerosis and their families.</p>	4.2

	The Committee heard from the clinical specialists that, as recommended in the Association of British Neurologists' guidelines, most patients who have had 2 relapses in the previous 2 years would be offered a disease-modifying therapy and enrolled in the risk-sharing scheme.	4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee recognised that a drug taken orally may give people with relapsing-remitting multiple sclerosis a valuable alternative to current first-line treatment options, but acknowledged comments from professional and patient groups that its twice-daily administration schedule may lower adherence compared with once-daily options.	4.24
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the clinical specialists that dimethyl fumarate would be considered as a treatment option in the same way as beta interferons or glatiramer acetate in people with relapsing-remitting multiple sclerosis eligible for active treatment under the Association of British Neurologists' guidelines.	4.4
Adverse reactions	The Committee considered that patients taking dimethyl fumarate experienced more gastrointestinal events and flushing, and skin reactions, particularly in the first months of treatment, than patients not taking dimethyl fumarate. The Committee concluded that, although dimethyl fumarate can lead to several different adverse reactions, it is generally well tolerated.	4.13
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee discussed the clinical-effectiveness evidence from 2 phase III randomised controlled trials: the DEFINE and CONFIRM trials.	4.6

<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee heard from the clinical specialists that the trial populations broadly represent patients who would be offered beta interferon or glatiramer acetate in the UK, in line with the Association of British Neurologists' guidelines.</p>	<p>4.6</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee concluded that, overall, the evidence suggested that dimethyl fumarate reduces relapses in people with relapsing-remitting multiple sclerosis compared with placebo, but that the magnitude of the treatment effect was unclear because the manufacturer did not justify its pre-specified covariate adjustment, because of the subjective nature of assessing the endpoint relapse, and because of the potential for functional unblinding.</p>	<p>4.6</p>
	<p>The Committee concluded that sustained disability progression confirmed for 6 months (rather than for 3 months) provides a more robust indication of the treatment effect, given that patients may recover from relapse.</p>	<p>4.9</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The Committee concluded that it had insufficient evidence from the manufacturer to recommend dimethyl fumarate in rapidly evolving severe, and highly active, relapsing-remitting multiple sclerosis.</p>	<p>4.12</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee noted that the results presented showed that dimethyl fumarate reduces relapses compared with placebo.</p>	<p>4.6</p>
	<p>The Committee noted that the manufacturer's mixed treatment comparison suggested that compared with placebo, dimethyl fumarate reduced confirmed disability progression sustained for 3 months, but not disability progression sustained for 6 months.</p>	<p>4.9</p>

	The Committee concluded that, compared with beta interferons and glatiramer acetate, dimethyl fumarate is more effective in reducing relapse rates and as effective for disability progression.	4.11
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee commented that the manufacturer had submitted a model structurally similarly to models used in previous NICE technology appraisals.	4.14
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the manufacturer modelled a waning of treatment effect because of the uncertain longer-term benefits of dimethyl fumarate. The Committee accepted the manufacturer's approach using the same rate of waning of effect for each treatment.	4.17
	The Committee heard from the Evidence Review Group (ERG) that several publications presented the annual costs by Expanded Disability Status Scale (EDSS) state and that, although they were also based on the UK Multiple Sclerosis Survey, they varied considerably. Some of the cost items were non-medical, and so it was unclear whether these items met the NICE reference case. The Committee highlighted its disappointment that all of the sources used by the manufacturer to estimate the cost of relapse were of low methodological quality.	4.18
	The Committee noted that the manufacturer and ERG were unable to explain any differences between the ICERs resulting from the manufacturer's model and from the model behind the risk-sharing scheme, and highlighted that there was still uncertainty related to the validity of the manufacturer's model.	4.22

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee concluded that additional health-related quality-of-life benefits associated with oral treatment and short washout duration may not have been fully captured within the manufacturer's economic modelling.</p>	<p>4.24</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>N/A</p>	<p>N/A</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The main drivers of the ICERs were the costs of treatment, how likely a patient was to experience disease progression, the probability of stopping treatment, and the magnitude of the treatment waning effect.</p>	<p>4.22</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee stated that considerable uncertainty remained associated with identifying which of the beta interferons and glatiramer acetate are relatively more cost effective when compared with dimethyl fumarate. The Committee also acknowledged that, when compared with dimethyl fumarate, Rebif-22 appeared to be the most cost-effective comparator in the manufacturer's analysis, and that Rebif-22 is a 'step-down' therapy for patients who cannot tolerate the higher dosage (that is, Rebif-44). Therefore, the Committee disregarded the comparison of dimethyl fumarate with Rebif-22, and considered the most plausible ICER to be based on a comparison of dimethyl fumarate with glatiramer acetate (the next most cost-effective comparator after Rebif-22) using the manufacturer's preferred scenario. The Committee concluded that, based on a comparison of dimethyl fumarate with glatiramer acetate, the most plausible ICER was likely to be below £27,700 per QALY gained, taking into consideration that waning of treatment effect may have been overestimated and also the benefits not captured in the economic modelling, such as the oral administration of dimethyl fumarate and its shorter washout period.</p>	<p>4.25</p>
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<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>The manufacturer of dimethyl fumarate has agreed a patient access scheme with the Department of Health. This is a simple discount scheme, with the discount applied at the point of purchase or invoice. The level of discount is commercial in confidence.</p>	<p>2.3</p>
<p>End-of-life considerations</p>	<p>N/A</p>	<p>-</p>

Equalities considerations and social value judgements	Potential equality issues raised during the appraisal were outside the remit of NICE technology appraisal guidance.	-
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5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has relapsing-remitting multiple sclerosis and the doctor responsible for their care thinks that dimethyl fumarate is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 The Department of Health and the manufacturer have agreed that dimethyl fumarate will be available to the NHS with a patient access scheme which makes dimethyl fumarate available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Biogen Idec medical information team on 0800 008 7401 or by email at biogenidec@professionalinformation.co.uk.
- 5.4 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- Costing template and report to estimate the national and local savings and costs associated with implementation.

6 Research Recommendations

- 6.1 The Committee recommends further research to better inform future cost-effectiveness models of relapsing-remitting multiple sclerosis. In particular, this research should include a more comprehensive synthesis of available evidence on the underlying disease progression of multiple sclerosis in the UK context, the impact of disability and relapses on preference-based measures of quality of life, and associated resource use and costs.

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review by the Guidance Executive when the review of NICE technology appraisal guidance 32, 127 and 254 has been published. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
August 2014

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Mark Chapman

Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Dr Neil Iosson

Locum General Practitioner

Terence Lewis

Lay member

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Elizabeth Murray

Reader in Primary Care, University College London

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University

Christopher O'Regan

Head of Health Technology Assessment & Outcomes Research, Merck Sharp & Dohme

Dr Sanjeev Patel

Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay member

Dr John Rodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

Roderick Smith

Chief Finance Officer, Coastal West Sussex Clinical Commissioning Group

Cliff Snelling

Lay member

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Martyn Burke

Technical Lead

Joanna Richardson

Technical Adviser

Jeremy Powell

Project Manager

9 Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the NHS Centre for Reviews and Dissemination and Centre for Health Economics, University of York:

- Norman G, Rice S, O'Connor J et al. (2013) Dimethyl fumarate for treating relapsing-remitting multiple sclerosis

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Biogen Idec

II Professional/specialist and patient/carer groups:

- Association of British Neurologists
- Multiple Sclerosis Society
- Multiple Sclerosis Trust
- Primary Care Neurology Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

- United Kingdom Multiple Sclerosis Specialist Nurse Association

III Other consultees:

- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Novartis
- Teva

C The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on dimethyl fumarate by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Jacqueline Palace, Consultant Neurologist and Honorary Senior Lecturer, Oxford University, nominated by Biogen Idec – clinical specialist
- Professor Neil Robertson, Professor of Neurology at Cardiff University and University Health Board, nominated by the Multiple Sclerosis Trust – clinical specialist
- Catherine John, nominated by the Multiple Sclerosis Trust – patient expert
- Nick Rijke, Director of Policy and Research, the Multiple Sclerosis Society, nominated by the Multiple Sclerosis Society – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Biogen Idec

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE [single technology appraisal](#) process.

It has been incorporated into the NICE pathway on [multiple sclerosis](#) along with other related guidance and products.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

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