

Teriflunomide 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

Minor changes to the recommendations have been made in line with NICE's current wording style. See [Changes after publication](#) for more information.

- 1.1 Teriflunomide 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 teriflunomide with the discount agreed in the patient access scheme.
- 1.2 People currently receiving treatment initiated within the NHS with teriflunomide 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 Teriflunomide (Aubagio, Genzyme) is an immunomodulatory disease-modifying therapy. It has a UK marketing authorisation for 'the treatment of adult patients with relapsing remitting multiple sclerosis'. It is anti-inflammatory and works by blocking proliferation of stimulated lymphocytes. The exact mechanism of action for teriflunomide is not fully understood. It is thought to reduce the number of activated lymphocytes, which would cause inflammation, and damage myelin in the central nervous system. Teriflunomide is taken orally as a 14 mg tablet once daily.
- 2.2 The summary of product characteristics lists the following adverse effects for teriflunomide: diarrhoea, alopecia, nausea and increased levels of alanine aminotransferase. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The manufacturer has stated that the list price of teriflunomide is £1037.84 per 28-tablet pack (excluding VAT). The length of teriflunomide treatment may vary because it is anticipated to be used continuously until a joint decision is made between the patient and clinician to stop treatment. Based on the list price, the manufacturer has estimated the annual cost of teriflunomide to be £13,529 per patient per year. Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of teriflunomide 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 the 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. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published.

3 The manufacturer's submission

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

Clinical effectiveness

3.1 The manufacturer provided clinical-effectiveness evidence, identified through systematic review, from:

- 3 phase III randomised controlled clinical trials: TEMSO (n=1088, 108 weeks follow-up), TENERE (n=324, follow-up between 48 and 118 weeks) and TOWER (n=1169, follow-up between 48 and 154 weeks)
- a phase II trial: Study 2001 (n=179, 36 weeks)
- 2 extension studies: to Study 2001 (n=147, median 7.1 years follow-up) and to TEMSO (n=742).

TEMSO, TOWER and Study 2001 compared the effectiveness of teriflunomide (7 mg or 14 mg once daily) with placebo. After completion of the core study for TEMSO and Study 2001, patients could enter the extension phases of the studies. Those who were originally randomised to teriflunomide continued their assigned treatment and those receiving placebo were re-allocated to teriflunomide 7 mg or 14 mg. TENERE compared the effectiveness of teriflunomide (7 mg or 14 mg once daily) with Rebif-44 (interferon beta-1a) 3 times a week. Each of the phase III multicentre trials included sites in the UK.

3.2 The inclusion criteria of TEMSO, TOWER and Study 2001 specified the number of previous relapses before study entry. For TEMSO and TOWER, this was at least 1 relapse in the previous year, or at least 2 in the previous 2 years. For Study 2001, this was 1 relapse in the previous year or 2 in the previous 3 years. The phase III trials included people with an Expanded Disability Status Scale (EDSS) score between 0 and 5.5, whereas Study 2001 and the extension studies had a range of between 0

and 6.0.

- 3.3 The primary outcome of TEMSO and TOWER was annualised relapse rate. The primary outcome of TENERE was time to failure (which included treatment failure and discontinuation), and the primary outcome of Study 2001 was combined unique active (new and persisting) lesions per MRI scan. The trial outcomes presented by the manufacturer included annualised relapse rate, severity of relapse (inferred from hospitalisation), disability (EDSS score, 3-month sustained accumulation of disability [SAD], and 6-month SAD), freedom from disease activity, mortality, adverse events and discontinuation rate. The manufacturer's meta-analysis of the placebo-controlled trials included 5 outcomes: annualised relapse rate, proportion of relapse-free patients, 3-month SAD, all-cause discontinuations and discontinuations because of adverse events. The intention-to-treat populations were used for analyses of clinical trial data.
- 3.4 The manufacturer provided data from Study 2001, TEMSO, TOWER and a meta-analysis, which compared the 14 mg dose of teriflunomide with placebo. Data from TEMSO, TOWER and the meta-analysis showed that teriflunomide was associated with a statistically significant reduction in adjusted annualised relapse rate (adjusted for EDSS score at baseline and geographic region) compared with placebo:
- TEMSO (teriflunomide 0.37 [95% confidence interval {CI} 0.31 to 0.44], placebo 0.54 [95% CI 0.47 to 0.62], 31.5% relative risk reduction, $p < 0.001$)
 - TOWER trial (teriflunomide 0.32 [95% CI 0.27 to 0.38], placebo not stated, relative risk 0.637 [95% CI 0.512 to 0.793], $p = 0.0001$)

- meta-analysis (relative risk compared with placebo 0.66, 95% CI 0.59 to 0.75).

Study 2001 showed that teriflunomide reduced the point estimate for the annualised relapse rate compared with placebo, but this was not statistically significant. TEMSO showed that statistically significantly fewer people receiving teriflunomide had 3-month SAD than those receiving placebo (teriflunomide: 20.2% [95% CI 15.6 to 24.7], placebo: 27.3% [95% CI 22.3 to 32.3], hazard ratio [HR] 0.70 [95% CI 0.51 to 0.97]). TOWER showed lower rates of 3-month SAD with teriflunomide than placebo at 48 weeks (teriflunomide: 7.8%, placebo: 14.2%) and at 132 weeks (teriflunomide: 15.8%, placebo: 21.0%). The meta-analysis of TEMSO and TOWER (Study 2001 was not included in this analysis) estimated a statistically significantly lower risk of 3-month SAD for teriflunomide compared with placebo (HR 0.694, 95% CI 0.544 to 0.886). Teriflunomide did not statistically significantly reduce 6-month SAD compared with placebo in TEMSO (HR 0.749; 95% CI 0.505 to 1.111) or TOWER (HR 0.843; 95% CI 0.533 to 1.334). No statistically significant differences in EDSS change from baseline were seen in the TEMSO and Study 2001 trials. Changes in EDSS from TOWER were provided as commercial in confidence by the manufacturer and therefore cannot be given here. The manufacturer also provided health-related quality-of-life data. Changes in fatigue and health-related quality of life (measured using SF-36 and EQ-5D) were not statistically significantly different between teriflunomide and placebo in the individual trials.

- 3.5 The primary outcome of TENERE was time to failure, defined as confirmed relapse or treatment discontinuation with teriflunomide 14 mg compared with Rebif-44. Of those receiving teriflunomide, 37.8% experienced failure compared with 42.4% in the Rebif-44 group. For the adjusted annualised relapse rate, no statistically significant differences between teriflunomide and Rebif-44 were reported in the TENERE study (0.259 compared with 0.216, respectively; $p=0.59$). The SAD data were provided as commercial in confidence and cannot be presented here. At week 48 the global satisfaction score on the Treatment Satisfaction Questionnaire for Medication was statistically significantly higher with teriflunomide than Rebif-44 (higher score indicates better satisfaction; 68.818 compared with 60.975, $p=0.0162$).
- 3.6 The manufacturer did a mixed treatment comparison (MTC) that compared teriflunomide with each of the treatments in the decision problem (beta interferons, glatiramer acetate, natalizumab and

fingolimod). The base-case MTC included 30 clinical trials, which recruited patients from the year 2000 onwards, at least 80% of whom had relapsing–remitting multiple sclerosis. A separate 'all years' analysis was also provided, which included all studies, including those that recruited patients before 2000. The year 2000 was justified by the manufacturer as an appropriate cut-off point because of changes in diagnostic criteria used in multiple sclerosis trials, which coincided with a reduction in annualised relapse rates at diagnosis. After 2000, the McDonald criteria were used, which identifies multiple sclerosis earlier than the previously used Poser criteria. The outcomes presented in the MTCs included annualised relapse rate, proportion of relapse-free patients, 3-month SAD, all-cause discontinuation rate, and discontinuation rate because of adverse events. The MTCs used a Bayesian random effects model. The results from the base-case MTC (post-2000) and 'all years' MTC are discussed for each comparator separately in sections 3.7 to 3.9.

3.7 The manufacturer provided data from the base-case MTC (post-2000) and on the clinical effectiveness of teriflunomide 14 mg compared with all the disease-modifying therapies including the interferons Rebif-44, Betaferon (interferon beta-1b) and Avonex (interferon beta-1a), as well as glatiramer acetate (see section 3.9 for the natalizumab and fingolimod results).

- For the annualised relapse rate, no statistically significant differences were seen between teriflunomide and Rebif-44 (rate ratio 1.06, 95% CI 0.84 to 1.35), Betaferon (rate ratio 0.98, 95% CI 0.73 to 1.31), Avonex (rate ratio 0.86, 95% CI 0.69 to 1.05) or glatiramer acetate (rate ratio 1.05, 95% CI 0.83 to 1.31).
- The base-case MTC (post-2000) also suggested no statistically significant difference in 3-month SAD between teriflunomide and Rebif-44 (HR 0.90, 95% CI 0.54 to 1.45), Betaferon (HR 0.58, 95% CI 0.30 to 1.12), Avonex (HR 0.77, 95% CI 0.50 to 1.24) or glatiramer acetate (HR 0.76, 95% CI 0.45 to 1.30).

- The base-case MTC (post-2000) also suggested there was a statistically significantly greater rate of all-cause discontinuation with teriflunomide compared with Betaferon (odds ratio 2.10, 95% CI 1.22 to 3.50) and glatiramer acetate (odds ratio 1.50, 95% CI 1.02 to 2.23). There was no statistically significant difference in discontinuation rate between teriflunomide and Rebif-44 (odds ratio 0.80, 95% CI 0.54 to 1.30) or Avonex (odds ratio 1.13, 95% CI 0.71 to 1.82).

3.8 The manufacturer also provided data from the 'all years' MTC on the clinical effectiveness of teriflunomide 14 mg compared with all the disease-modifying therapies including the interferons Rebif-44, Betaferon (interferon beta-1b) and Avonex (interferon beta-1a), and glatiramer acetate.

- For the annualised relapse rate, no statistically significant differences were seen between teriflunomide and Rebif-44 (rate ratio 1.04, 95% CI 0.84 to 1.28), Betaferon (rate ratio 0.97, 95% CI 0.80 to 1.18), Avonex (rate ratio 0.84, 95% CI 0.71 to 1.00) or glatiramer acetate (rate ratio 1.01, 95% CI 0.85 to 1.21).
- The 'all years' MTC also showed no statistically significant difference in 3-month SAD between teriflunomide and Rebif-44 (HR 0.97, 95% CI 0.66 to 1.43), Betaferon (HR 0.75, 95% CI 0.49 to 1.24), Avonex (HR 0.80, 95% CI 0.51 to 1.23) or glatiramer acetate (HR 0.90, 95% CI 0.60 to 1.37).
- The 'all years' MTC showed there was not a statistically significant difference in all-cause discontinuation between teriflunomide compared with Rebif-44 (odds ratio 0.74, 95% CI 0.51 to 1.10), Betaferon (odds ratio 1.56, 95% CI 0.95 to 2.49), Avonex (odds ratio 1.04, 95% CI 0.66 to 1.60) or glatiramer acetate (odds ratio 1.28, 95% CI 0.89 to 1.84).

3.9 The base-case MTC (post-2000) and 'all years' MTC were also used to compare the clinical effectiveness of teriflunomide with fingolimod and natalizumab for the whole active relapsing–remitting multiple sclerosis population. The base-case MTC (post-2000) suggested that teriflunomide was associated with a statistically significantly higher annualised relapse rate compared with fingolimod (rate ratio 1.45, 95% CI 1.17 to 1.80) and natalizumab (rate ratio 2.12, 95% CI 1.63 to 2.75). This was also seen with the 'all years' MTC. Both the base-case MTC (post-2000) and 'all years' MTC showed that there was no statistically significant difference in 3-month SAD between teriflunomide and

fingolimod or natalizumab. The manufacturer also presented data for the following outcomes: proportion of patients who were relapse-free; all-cause discontinuation; and discontinuation because of adverse events.

- 3.10 The manufacturer conducted 2 separate indirect comparisons of teriflunomide for the subgroups of patients in TEMSO with highly active relapsing–remitting multiple sclerosis (teriflunomide n=11, placebo n=10; approximately 2% of the trial population) and rapidly evolving severe relapsing–remitting multiple sclerosis (teriflunomide n=33, placebo n=39; approximately 7% of the trial population). The indirect comparison used data from the fingolimod European public assessment report and the natalizumab manufacturer's submission to NICE. The outcomes presented included annualised relapse rate and 3-month SAD. The 95% confidence intervals and probability (p) values were not provided and the detailed results of these analyses were provided but were marked as commercial in confidence and therefore cannot be presented here. The indirect treatment comparisons suggested that teriflunomide was associated with a lower annualised relapse rate and 3-month SAD compared with fingolimod in highly active relapsing–remitting multiple sclerosis. It also suggested that teriflunomide was associated with a lower annualised relapse rate, but a higher 3-month SAD than natalizumab in rapidly evolving severe relapsing–remitting multiple sclerosis.
- 3.11 The manufacturer stated that almost all patients treated with teriflunomide reported at least 1 adverse event. However, for most of the events, the incidence was similar to placebo. Rates of discontinuation because of adverse events were higher for teriflunomide than with placebo. The manufacturer provided results from the base-case MTC (post-2000) and 'all years' MTC for all-cause discontinuations (see sections 3.7 and 3.8). Discontinuations because of adverse events were presented as academic in confidence and cannot be reported here. The base-case (post-2000) MTC and 'all years' MTC showed that there was no statistically significant difference in discontinuation because of adverse events between teriflunomide and Betaferon, Avonex, Rebif-44 or glatiramer acetate. In addition, the manufacturer carried out a comparison of adverse events between teriflunomide and Rebif-44, the results of which were provided as commercial in confidence and

therefore cannot be presented here.

Cost effectiveness

- 3.12 The manufacturer submitted an economic model to evaluate the cost effectiveness of teriflunomide. In addition, it conducted a systematic literature review that identified 2 cost-effectiveness studies for relapsing–remitting multiple sclerosis to inform parameters used in the model.
- 3.13 The manufacturer's model used a multistate Markov approach. The model contained 20 health states that were defined by disability level (EDSS scores 0–9), and the type of multiple sclerosis (relapsing–remitting multiple sclerosis or secondary progressive multiple sclerosis). Patients with relapsing–remitting multiple sclerosis entered the model in relapsing–remitting multiple sclerosis states 0–7. In each cycle, patients could remain in the same state, progress to a worse state (patients could not regress to a better state), transfer to a secondary progressive multiple sclerosis health state, or die. Health states for secondary progressive multiple sclerosis were included to represent the clinical progression of relapsing–remitting multiple sclerosis. It was assumed that, when progressing from relapsing–remitting multiple sclerosis to a secondary progressive multiple sclerosis state, the patient's disease would also progress by 1 EDSS state. In addition, in each cycle patients could withdraw from treatment, stop treatment after reaching the EDSS limit for which a disease-modifying treatment is allowed (EDSS 6), or experience relapse and adverse events. The probability of death depended on the EDSS state, age and sex. The transition probabilities, discontinuation rates, relapse rates and adverse event rates throughout the model were based on data from the base-case MTC (post-2000) (treatment effect on progression, treatment effect on relapses, hospitalisation because of relapse, withdrawal, and adverse events), or taken from the literature (natural disease progression, demographic profile of patients entering the model, natural relapse rates, mortality). Treatment effects on disability and relapse were assumed to be constant over time, that is, there was no waning of treatment effect and, once patients stopped receiving treatment, they continued to benefit because they were at a better EDSS state than they would have been without the

treatment, and the EDSS state determined disability, relapse and progression. The patients then followed the natural history of progression. In the base case, patients stopped treatment if their relapsing–remitting multiple sclerosis progressed to secondary progressive multiple sclerosis, or progressed to an EDSS state greater than 6. In the manufacturer's sensitivity analyses, treatment could be continued in secondary progressive multiple sclerosis but the treatment effect was reduced by 50% when the condition progressed to secondary progressive multiple sclerosis. It was assumed that withdrawal rates would not persist over the whole period of the model and therefore after 2 years the rate was estimated to decrease by 50% (based on clinical opinion). The cycle length was 1 year, and the time horizon was lifetime, assumed to be 50 years with a mean starting age of 39 years (based on the UK risk-sharing scheme cohort). The manufacturer stated that the analyses used an NHS and personal and social services perspective and applied a 3.5% discount rate on costs and health effects.

- 3.14 The manufacturer's base-case analyses compared teriflunomide with a blended comparator of Rebif-22 (interferon beta-1a [22 micrograms]), Rebif-44, Avonex, Betaferon and glatiramer acetate. The blended comparator was calculated as the weighted average of the clinical efficacy and cost–utility inputs on the basis of UK market share data. The manufacturer also conducted a full incremental analysis, comparing teriflunomide with the individual treatments: glatiramer acetate, Rebif-22, Rebif-44, Avonex, Betaferon and aggregated Rebif. The possibility of receiving more than 1 treatment (treatment sequencing) was considered in scenario analyses (see section 3.19). The manufacturer provided separate analyses of teriflunomide compared with fingolimod and natalizumab for the people with relapsing–remitting multiple sclerosis, and for the subgroups with highly active relapsing–remitting multiple sclerosis and with rapidly evolving severe relapsing–remitting multiple sclerosis (see section 3.21).
- 3.15 The model applied health state utility values to each of the EDSS states. The utility values in the manufacturer's model were taken from Orme et al. (2007), which was a UK survey of health-related quality of life (measured using EQ-5D) in people with multiple sclerosis. The utility values ranged from 0.870 (EDSS 0) to a state valued as worse than

death, -0.049 (EDSS 8) and -0.195 (EDSS 9), by the general population sample who provided values for the EQ-5D. The secondary progressive multiple sclerosis health states were the values from the relapsing–remitting multiple sclerosis health states minus 0.045 . The manufacturer collected EQ-5D data in the TEMSO study but did not apply these data in the model on the basis that this study was an international study and may not be representative of the UK population. Disutility values were also applied to each EDSS state for relapse, caregiving and adverse events. The disutilities associated with relapse were estimated using a UK study (Orme et al.) and a US study (Prosser et al. 2003). The UK disutility value of relapse taken from Orme et al. was assumed to represent relapse without hospitalisation. The difference in utility seen between relapses with or without hospitalisation in the Prosser study was then used to estimate the disutility of relapse with hospitalisation (-0.0297 , -0.0089 without hospitalisation). Disutility values taken from a study by Gani et al. (2008) were applied for caregivers and took into account the time spent caring for the patient (which was taken from Orme et al.). A different value was estimated for each EDSS state and ranged from 0 (EDSS 0) to -0.140 (EDSS 9). The disutility values for adverse events were taken from the published literature. A value was derived for each event and adjusted for time, according to the treatment, to estimate a treatment-specific annual disutility value; these included nausea (-0.0001), diarrhoea (-0.0004), hair thinning (-0.1140), fatigue (-0.0014), headache (-0.0002), immediate post-injection systemic reactions (-0.0001), arthralgia (-0.0034) and influenza-like symptoms (-0.0343 to -0.0114).

- 3.16 The model used NHS reference costs and the Payment by Results tariff to estimate the costs of administration, monitoring and adverse effects associated with each treatment. The manufacturer assumed that teriflunomide was not associated with administration costs because it is an oral treatment. In addition, some costs were derived from the literature; health-state costs (including direct medical costs and direct non-medical costs) were derived from Tyas et al. (2007). These costs differed across the EDSS states and ranged from £336 (EDSS 0) to £19,704 (EDSS 9) for direct medical costs, and from £5335 (EDSS 0) to £20,811 (EDSS 8) and £12,915 (EDSS 9) for non-medical costs. The cost associated with relapse was sourced from Dee et al. (2012): £845

without hospitalisation and £6164 with hospitalisation. The resource use and costs applied in the model were validated by the manufacturer's clinical experts. Fingolimod is available to the NHS with a simple discount through a patient access scheme agreed with the Department of Health. However, the magnitude of this discount was not known by the manufacturer and therefore was not applied in the base-case analysis (but was explored in the sensitivity analysis, using a range of assumed discounts).

- 3.17 Teriflunomide dominated the blended comparator in the base case (incremental costs: –£5491; incremental quality-adjusted life years [QALYs]: 0.201), that is, it was less expensive and more effective. The cost-effectiveness acceptability curve provided by the manufacturer showed a 63% probability of teriflunomide being cost effective if the maximum acceptable incremental cost-effectiveness ratio (ICER) was £20,000 per QALY gained.
- 3.18 The manufacturer conducted one-way sensitivity analyses, which showed that the cost effectiveness of teriflunomide was most sensitive to the blended comparator hazard ratio for disability progression, the teriflunomide hazard ratio for disability progression, the blended comparator withdrawal rate, disease costs, the teriflunomide annual relapse rates, and the blended comparator annual relapse rates. For each of the analyses, teriflunomide continued to dominate the blended comparator, except when the hazard ratios for disability progression were varied. Teriflunomide was dominated by the blended comparator when the lower 95% confidence interval for the blended comparator disability progression hazard ratio was applied (that is, reducing the progression risk with the blended comparator). When applying the upper 95% confidence interval for the teriflunomide disability progression hazard ratio (that is, increasing the progression risk with teriflunomide), the ICER for teriflunomide compared with the blended comparator was £20,613 per QALY gained.
- 3.19 The manufacturer conducted scenario analyses that explored likely treatment sequences, based on clinical opinion. This analysis included a sequence of 2 treatments after teriflunomide or the blended comparator. Treatments that were included as second and third line were the blended

comparator, fingolimod, natalizumab or best supportive care. As part of these analyses, the manufacturer applied 2 assumed patient access scheme prices for fingolimod (£11,000 and £13,000), as well as the list price. Teriflunomide dominated the blended comparator in all scenarios, irrespective of the size of patient access scheme discount for fingolimod. The manufacturer conducted further scenario analyses including using the 'all years' MTC for clinical data, using different sources of costs and utilities, and using the EDSS distribution, patient population and proportion of relapses from the clinical trials. Teriflunomide dominated the blended comparator for all scenarios.

- 3.20 The manufacturer also presented an incremental analysis in which teriflunomide was compared with the individual comparators (glatiramer acetate, Rebif-22, Rebif-44, Avonex and Betaferon). In the base case, teriflunomide dominated all the comparators. The manufacturer also conducted incremental analysis for the following scenarios: the 'all years' MTC data; the 'all years' MTC values without Bornstein et al. (1987; this study was excluded because it did not use EDSS); and the base-case MTC (post-2000) values including treatment in secondary progressive multiple sclerosis. Teriflunomide dominated each of the individual comparators for most of the scenarios, with the following exceptions: the 'all years' MTC (£86,866 per QALY gained for teriflunomide compared with glatiramer acetate [incremental costs: £3573; incremental QALYs: 0.041]); the 'all years' MTC without Bornstein et al. (£21,062 per QALY gained for teriflunomide compared with glatiramer acetate [incremental costs: £2641; incremental QALYs: 0.125], and £301,857 per QALY gained for Rebif-22 compared with teriflunomide [incremental costs: £4130; incremental QALYs: 0.130]); and the base-case MTC (post-2000) with secondary progressive multiple sclerosis treatment (£105,604 per QALY gained for Rebif-22 compared with teriflunomide [incremental costs: £11,709; incremental QALYs: 0.111]).
- 3.21 The manufacturer presented cost-effectiveness results for 2 subgroups: teriflunomide compared with fingolimod in the subgroup of people with highly active relapsing–remitting multiple sclerosis, and teriflunomide compared with natalizumab in the subgroup of people with rapidly evolving severe relapsing–remitting multiple sclerosis. For the first subgroup, teriflunomide dominated fingolimod when the fingolimod list

price was used (incremental cost savings: £35,084; incremental QALYs: 0.746) and when it was assumed fingolimod cost £11,000 per year (incremental cost savings: £67,826; incremental QALYs: 0.725). For the second subgroup, teriflunomide was associated with an ICER of £63,107 (incremental cost savings: £30,133; incremental QALYs: –0.477) saved per QALY lost compared with natalizumab. The manufacturer stated that, because of limitations in the clinical data (see section 3.10), these analyses were not reliable.

Evidence Review Group comments

- 3.22 The ERG reviewed the decision problem presented by the manufacturer, and commented that it was in line with the scope, except for the population. The ERG noted that secondary progressive multiple sclerosis and primary progressive multiple sclerosis populations were not presented in the manufacturer's submission because the marketing authorisation for teriflunomide was limited to relapsing–remitting multiple sclerosis.
- 3.23 The ERG considered the generalisability of the placebo-controlled clinical trials to UK clinical practice. It noted that although most of the patients in the trials had relapsing–remitting multiple sclerosis (at least 87%), the trials also included people with primary progressive multiple sclerosis and secondary progressive multiple sclerosis. The ERG noted that Study 2001 used the Poser rather than McDonald criteria to diagnose patients with multiple sclerosis, and stated that the McDonald criteria were more in keeping with current clinical practice. However, it concluded that overall, the differences were not large and that the trial populations can be considered generalisable to the UK population with active relapsing–remitting multiple sclerosis who would be receiving a disease-modifying therapy.
- 3.24 The ERG commented that all placebo-controlled clinical trials were short considering the generally long duration of multiple sclerosis and infrequency of relapses, and therefore may not adequately capture differences in relapse rates. Of particular note, Study 2001 lasted only 36 weeks. The ERG noted that the European Medicines Agency suggests that a trial duration of at least 2 years is needed to accurately assess

relapses and disability progression. Furthermore, the ERG noted that quality-of-life and mortality data were limited to 2-year follow-up and supplemented by longer-term extension studies, which were not placebo controlled and therefore did not account for the natural history of the disease.

3.25 The ERG noted that the TEMSO and TOWER trials reported 3-month SAD and that the European Medicines Agency recommends the use of 6-month SAD data. The ERG commented that 6-month SAD would be preferable to 3-month SAD because there remains a possibility of recovery from disability at 3 months. The ERG noted that the manufacturer provided evidence that a large proportion of patients in both groups of the trials did not have persistent disability (that is, their disability regressed). The ERG commented that meta-analysis of 6-month SAD was not provided by the manufacturer.

3.26 The ERG commented that a random effects model chosen by the manufacturer for meta-analyses of the placebo-controlled trials may not have been appropriate because of the small number of studies (2 or 3 in each analysis). The ERG noted that there were some differences between Study 2001 and the phase III trials TEMSO and TOWER. It also noted that a higher proportion of patients in Study 2001 had received previous disease-modifying therapies compared with TEMSO and TOWER. It noted that Study 2001, as a proof of concept study, was small (61 patients per treatment arm) and just 36 weeks long, so assessment of relapse rates may not have been robust. Furthermore, it noted that EDSS scores were higher and more patients stopped treatment in the teriflunomide arm of Study 2001 than in the other trials. The ERG stated that these differences suggested that the studies were too heterogeneous to pool the results of Study 2001 with TOWER and TEMSO. It noted that Study 2001 was excluded from the 3-month SAD meta-analysis because of the short duration of this trial. The ERG commented that it was questionable whether Study 2001 should have been included in the analyses for the other outcomes because of its short duration and the differences between the arms in previous treatment.

3.27 The ERG noted that the TENERE trial may not have been adequately

powered to detect statistically significant differences in all investigated outcomes. It commented that because TENERE was not a double-blind trial, there may be bias in the evaluation of the primary outcome (which relies on patient-reported symptoms). The ERG also noted that there were some differences in patient baseline characteristics between the 2 treatment arms, which make the results of the trial difficult to interpret (details were provided as commercial in confidence and therefore cannot be presented here).

- 3.28 The ERG noted that the base-case MTC (post-2000) included all relevant comparators. Informal checks for consistency by the ERG did not identify major problems, but the ERG commented that comparison of Betaferon with placebo showed different 3-month SAD results in the base-case MTC (post-2000) to those from the TENERE study. The ERG noted that the base-case MTC (post-2000) data showed that Betaferon was associated with a higher 3-month SAD than placebo. The 3-month SAD data from the TENERE study were provided as commercial in confidence and cannot be presented here. In addition, the ERG stated that the difference between the direct comparison and the base-case MTC (post-2000) was quite large for the effect of teriflunomide on 3-month SAD compared with Rebif-44. The ERG noted that this inconsistency may have contributed to the favourable results for teriflunomide compared with the beta interferons generated by the MTC (particularly for the base-case analysis). It also noted that the results of the 'all years' MTC were more consistent with the direct trial results. The ERG commented that the relative effect of teriflunomide on 3-month SAD was a key driver in the economic model.
- 3.29 The ERG's major criticism of the manufacturer's MTC was that pre-2000 trials were excluded in the base-case analysis. It acknowledged the reasons given by the manufacturer (change in diagnostic criteria in 2000 from Poser to McDonald, and identification of patients earlier in the disease course). However, the ERG noted that the base-case MTC (post-2000) included 5 studies that had used the earlier Poser criteria. The ERG considered that a more appropriate approach would have been to conduct an 'all years' MTC with baseline relapse rate included as a covariate because it would have included all the trial data but would have accounted for any heterogeneity in baseline annualised relapsed rates.

The ERG noted that the impact of the 2000 cut-off date was that all but 1 of the placebo-controlled trials of beta interferons and glatiramer acetate were excluded. It commented that although the manufacturer's concerns about including older trials were justified to some extent, neither the base case nor the 'all years' analysis were optimal, and that omission of the placebo-controlled beta interferon trials from the base-case analysis reduced the reliability of the results.

- 3.30 The ERG reviewed the trials that were included in the MTC and noted that some were short in both the base-case and the 'all years' networks. For example, the network for the outcome of annualised relapse rate included 11 trials of less than or equal to 12 months' duration. The network for the outcome of 3-month SAD included 3 trials of less than or equal to 12 months' duration. The ERG again commented that 12 months is a short duration for assessing infrequent events such as multiple sclerosis relapse or confirmed progression. However, the ERG did not re-run the MTC analyses after excluding these trials of shorter duration. It commented that it was unclear what impact this may have, especially considering outcomes such as relapse and SAD.
- 3.31 The ERG reviewed the evidence provided for the subgroups of people with highly active or rapidly evolving severe relapsing–remitting multiple sclerosis. It commented that these results were not reliable because of the very small number of patients in this subgroup from the TEMSO trial and the poor definition of these patients used in the TOWER trial. The ERG noted that the manufacturer's submission did not include a synthesis of adverse event data that could be readily checked against supporting tables. Furthermore, the relatively short duration of the placebo-controlled trials limited the assessment of any differences in mortality and less frequently reported adverse events. The ERG commented further that although a greater number of patients in the Rebif-44 arm in the TENERE trial stopped treatment because of adverse events, this should be interpreted in the light of differences in baseline characteristics (the details of which were provided as commercial in confidence and therefore cannot be presented here). The ERG commented that the impact of this difference is unknown.
- 3.32 The ERG reviewed the manufacturer's economic model and systematic

review. It commented that the manufacturer did a comprehensive, well-rounded systematic literature review and that the model was structurally similar to models used in previous NICE technology appraisals. During clarification, an error was identified in the manufacturer's model, which was corrected throughout the ERG analyses.

3.33 The ERG conducted some sensitivity analyses to determine the key areas of uncertainty in the manufacturer's model. It identified the following as having the most impact and conducted scenario analyses to explore them further:

- the choice of comparator (see section 3.34)
- the natural history and the rate of transition to secondary progressive multiple sclerosis (see section 3.35)
- the rate of progression (see section 3.36)
- the health-related quality of life associated with the more severe health states (see section 3.38).

3.34 The ERG regarded the use of a blended comparator in the base case of the manufacturer's model as inappropriate. The manufacturer's method for calculating the blended comparator, which used a weighted average of each individual treatment outcome as model inputs, was considered by the ERG to be inappropriate, because the outcomes of the average treatment effects are not the same as the average outcomes of the treatments because of the correlation between the costs and QALYs in the model. To address this, the ERG weighted the costs and QALYs for each individual treatment, the results of which were provided as commercial in confidence by the manufacturer and therefore cannot be presented here. Overall, the ERG considered that the use of a blended comparator hides the effects of changes in the model because the different individual treatments may have different treatment effects compared with placebo.

3.35 The ERG reviewed how disability progression was captured in the manufacturer's model. It noted that the model used the London Ontario data set (published in 1989) for predicting the initial distribution of EDSS and natural history progression of relapsing–remitting multiple sclerosis

without treatment. The ERG stated that previous NICE technology appraisals have questioned the applicability of the London Ontario data set because of changes in multiple sclerosis care and because it did not collect data on patients whose condition improved to a better EDSS state over time. The ERG noted that a substantial proportion of patients in the TEMSO trial who experienced SAD later improved. It also considered that the initial EDSS states and transition probabilities were taken from a population with more severe disease than the population in which teriflunomide is expected to be used. The ERG therefore conducted analyses to explore each of the following:

- using the initial EDSS distribution from the TEMSO and TOWER trials
- using the TEMSO and TOWER data to estimate disability progression in 2 analyses: patients with active relapsing–remitting multiple sclerosis, and patients with secondary progressive multiple sclerosis
- using alternative rates of conversion from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis based on the London Ontario data set, calculated by the ERG.

With the patient access scheme discount was applied, teriflunomide dominated Rebif and the blended comparator for each of these disability progression scenarios.

3.36 The ERG noted that the effect of treatment on disability progression was estimated from the manufacturer's base-case MTC (post-2000), and stated that these data were not robust because a large number of studies were excluded (by selecting only studies post-2000) and because of the heterogeneity across the included studies (see sections 3.28 to 3.30). The ERG highlighted the following concerns:

- Betaferon was estimated to be less effective at slowing disability progression compared with best supportive care.
- The estimate of 3-month SAD for teriflunomide compared with Rebif-44 from the base-case MTC (post-2000) appeared to be more favourable towards teriflunomide compared with the direct head-to-head evidence in TENERE.

- The blended comparator masked treatment effects and subsequently favoured teriflunomide compared with each of the beta interferons individually.

3.37 The ERG conducted scenario analyses to explore the impact of different treatment effects. Firstly, it used the TENERE trial data, rather than MTC data, to estimate the relative treatment effect for teriflunomide compared with Rebif-44. Secondly, it tested the assumption that there was no difference in treatment effect between teriflunomide and Rebif-44. Finally the 'all years' MTC data were used to estimate the relative treatment effect of teriflunomide. Applying the patient access scheme price in these exploratory analyses, teriflunomide dominated the blended comparator or Rebif-44 in all scenarios.

3.38 The ERG commented on the utility values used in the model. It noted that the manufacturer's base case used values derived from a 2005 UK multiple sclerosis survey (Orme et al. 2007), which have been criticised in previous NICE technology appraisals because of the low response rates, selection bias, unrepresentative population and patient-reported level of severity. The ERG noted that the TEMSO trial had collected health-related quality-of-life data using EQ-5D, although only for EDSS states 0–6. The ERG noted that the utility values from TEMSO were higher for all EDSS states than the estimates taken from Orme et al., which were the lowest values identified in the manufacturer's literature review. The ERG considered the utility values from TEMSO to be more applicable to the treatment population because TEMSO better reflected patients who are likely to receive teriflunomide as a treatment for active relapsing–remitting multiple sclerosis. The ERG therefore explored 4 scenarios using alternative utility values:

- TEMSO data for EDSS state 0–6, and health-related quality-of-life data from Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (NICE technology appraisal guidance 127) for EDSS states 7–9
- TEMSO data for EDSS states 0–6, and an average of 4 studies for states 7–9
- an average of 4 studies used for all EDSS states

- TEMSO data for EDSS states 0–6, and the differences between states 7–9 seen in Orme et al. used to calculate states 7–9 from the TEMSO data.

Applying the patient access scheme price, teriflunomide dominated the blended comparator and Rebif-44 in all scenarios. The ERG considered that the last scenario was the most representative of patients being treated with teriflunomide because it used utility data from the TEMSO trial (EDSS 0–6) for the baseline estimates of health-related quality of life and estimated utility differences between EDSS states 7–9 from a large UK-based survey (Orme et al.).

3.39 The ERG reviewed the costs included in the manufacturer's model. It commented that there was uncertainty surrounding which costs were included in some of the sources used, particularly the direct non-health costs for the EDSS states. Furthermore, it noted that one source of costs (Karampampa et al. 2012, used in sensitivity analyses) included informal care costs such as productivity losses of the working caregivers, and that these do not meet the NICE reference case. When the ERG investigated the impact of excluding non-health costs, teriflunomide still dominated the blended comparator and Rebif-44 when the patient access scheme discount was included.

3.40 The ERG presented an exploratory analysis comprising all of its preferred parameters, as follows:

- trial distribution of initial EDSS
- trial estimates of natural history
- ERG calculation of secondary progressive multiple sclerosis conversion
- treatment effects from the 'all years' MTC
- trial-based health-related quality-of-life data using the differences seen in the Orme et al. (2007) study to extrapolate the higher EDSS state values

- exclusion of non-health costs.

The resulting ICERs were similar to those in the manufacturer's base case, although the total QALYs were higher and the total costs lower for each intervention. The ERG noted that the increase in total QALYs was because the EDSS states were less severe at the start of treatment, the model allows for improvements in disability (EDSS), and because utility values were derived from the trials (for EDSS 0–6). The decrease in total costs was largely explained by the exclusion of non-health costs. The results of the ERG's probabilistic analysis suggested that teriflunomide is more effective and more costly than glatiramer acetate, resulting in an ICER of £107,148 per QALY gained. However, teriflunomide dominated Rebif-44 and the blended comparator. Because of the uncertainty associated with the manufacturer's MTC, the ERG also presented its preferred analysis using the manufacturer's base-case MTC (post-2000), rather than the 'all years' MTC. As described in sections 3.28 to 3.30, by using the base-case MTC (post-2000) rather than direct trial results, Betaferon is less effective (in terms of 3-month SAD) than placebo. In addition, the hazard ratios comparing teriflunomide with each of the comparators are lower in the base-case MTC (post-2000), and therefore more favourable to teriflunomide. The ERG's deterministic analysis resulted in an ICER of £6266 per QALY gained for teriflunomide compared with glatiramer acetate, and teriflunomide dominated all other comparators.

- 3.41 The ERG noted the treatment became more cost effective as more patients stopped treatment (that is, higher withdrawal rates reduced the ICER), and suggested that this is counterintuitive. The ERG conducted exploratory analyses to test for logical consistency and external validation of the manufacturer's model. The ERG compared the change in QALYs, the change in costs and the ICERs, compared with treatment without a disease-modifying therapy presented in previous NICE technology appraisals ([Beta interferon and glatiramer acetate for the treatment of multiple sclerosis \[NICE technology appraisal guidance 32\]](#), [Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis \[NICE technology appraisal guidance 127\]](#), and [Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis \[NICE technology appraisal guidance 254\]](#)). It noted that the manufacturer's model estimated ICERs for the interferons and glatiramer acetate compared with treatment without disease-modifying therapy that were considerably higher than

those presented for the UK risk-sharing scheme (Avonex: £175,918 per QALY gained; Betaferon: dominated by treatment without disease-modifying treatment; Rebif-22: £82,098 per QALY gained; Rebif-44: £79,310 per QALY gained; glatiramer acetate: £142,703 per QALY gained), and that the ICER for teriflunomide compared with treatment without disease-modifying therapy was substantially lower than these ICERs.

3.42 The ERG commented on the subgroup analyses that compared teriflunomide with fingolimod and natalizumab for highly active relapsing–remitting and rapidly evolving severe relapsing–remitting multiple sclerosis, respectively. It did not consider the subgroup analyses to be reliable because of the very small number of patients included in each of the teriflunomide groups, because the relative risks and hazard ratios were calculated from the specified subgroups combined with the natural history of the full relapsing–remitting multiple sclerosis population, because only results from the TEMSO trial were used to calculate the teriflunomide effects and because of the inadequate methodology used. The ERG also noted that, although the manufacturer stated that the patient population in the model was based on patients for whom beta interferons and glatiramer acetate were the appropriate comparators (that is, not in people with rapidly evolving severe or highly active relapsing–remitting multiple sclerosis), the manufacturer did not provide subgroup analyses that excluded people with rapidly evolving severe or highly active relapsing–remitting multiple sclerosis. The ERG used the manufacturer's corrected model, and assumed that teriflunomide in people with rapidly evolving severe or highly active relapsing–remitting multiple sclerosis has the same effectiveness as in the full active relapsing–remitting multiple sclerosis population, to calculate the ICERs for teriflunomide in people with rapidly evolving severe or highly active relapsing–remitting multiple sclerosis populations (that is, compared with natalizumab and fingolimod respectively). The patient access scheme price for fingolimod was not applied. When the patient access scheme for teriflunomide was included, teriflunomide was associated with a lower cost than both natalizumab and fingolimod, but also with fewer QALYs.

Manufacturer's additional evidence

3.43 The manufacturer provided additional evidence, as requested in the appraisal consultation document, during the consultation. The manufacturer presented results of the 'all years' MTC, adjusted for baseline relapse rates. These data were similar to the 'all years' MTC (see section 3.8). These data compared the clinical effectiveness of teriflunomide 14 mg with all the disease-modifying therapies, including the interferons (Rebif-44, Betaferon and Avonex), glatiramer acetate, fingolimod and natalizumab for the whole relapsing–remitting multiple sclerosis population.

- For the annualised relapse rate, no statistically significant differences were seen between teriflunomide and Rebif-44 (rate ratio 0.99, 95% CI 0.77 to 1.30), Betaferon (rate ratio 0.94, 95% CI 0.72 to 1.25), Avonex (rate ratio 0.78, 95% CI 0.61 to 1.01) or glatiramer acetate (rate ratio 0.99, 95% CI 0.79 to 1.24). Teriflunomide was associated with a statistically significantly higher relapse rate than fingolimod (rate ratio 1.41, 95% CI 1.14 to 1.77) and natalizumab (rate ratio 2.10, 95% CI 1.61 to 2.76).
- The adjusted 'all years' MTC also showed no statistically significant difference in 3-month SAD between teriflunomide and Rebif-44 (HR 0.82, 95% CI 0.54 to 1.27), Betaferon (HR 0.59, 95% CI 0.34 to 1.03), Avonex (HR 0.72, 95% CI 0.46 to 1.16), glatiramer acetate (HR 0.76, 95% CI 0.49 to 1.20), fingolimod (HR 0.91, 95% CI 0.63 to 1.29) or natalizumab (HR 1.14, 95% CI 0.73 to 1.8).
- The adjusted 'all years' MTC showed there was a statistically significantly greater rate of all-cause discontinuation with teriflunomide compared with Betaferon (odds ratio 1.93, 95% CI 1.19 to 3.04), glatiramer acetate (odds ratio 1.47, 95% CI 1.02 to 2.05) and fingolimod (odds ratio 1.52, 95% CI 1.01 to 2.17). There was no statistically significant difference in discontinuation rate between teriflunomide and Rebif-44 (odds ratio 0.88, 95% CI 0.60 to 1.26), Avonex (odds ratio 1.18, 95% CI 0.74 to 1.84) or natalizumab (odds ratio 1.34, 95% CI 0.82 to 2.22).

The manufacturer also presented data for the proportion of patients who were relapse-free. However, these data are marked as academic in confidence by the manufacturer and cannot be presented here.

- 3.44 The manufacturer provided a revised cost-effectiveness base case as part of the additional evidence, which did all of the following:
- used the 'all years' MTC adjusted for baseline relapse rates to estimate disease progression and withdrawal rates
 - used the natural history progression data from the placebo arms of the TOWER and TEMSO trials
 - used the baseline characteristics and initial EDSS distribution from the TOWER and TEMSO trials
 - used the ERG's amended calculation for SPMS conversion probabilities
 - excluded the direct non-medical costs
 - used the utilities seen in the TEMSO trial, using increments from the Orme et al. (2007) study for high EDSS states when trial data were not available
 - applied treatment waning whereby the treatment effect was 75% after 2 years and 50% after 5 years.

The manufacturer presented a fully incremental analysis using the revised base case that showed teriflunomide dominated each of the beta interferons. Compared with glatiramer acetate, teriflunomide had an ICER of £13,234 per QALY gained.

- 3.45 The additional evidence provided by the manufacturer also included sensitivity analyses for which the manufacturer presented pairwise comparisons with glatiramer acetate. In the revised base case (see section 3.44), treatment waning was included, and non-medical costs were excluded. The manufacturer presented sensitivity analyses to explore the impact of these. When treatment waning and non-medical costs were both excluded, the probabilistic ICER of teriflunomide compared with glatiramer acetate was £10,143 per QALY gained. When non-medical costs were included, teriflunomide dominated glatiramer acetate irrespective of whether treatment waning was or was not applied.

- 3.46 The manufacturer provided sensitivity analyses relating to treatment sequencing in the additional evidence. The manufacturer presented

7 different scenarios. The sequences that included teriflunomide dominated the sequences without teriflunomide in 5 of the 7 scenarios. These 5 sequences had teriflunomide replacing a line of treatment (for example, teriflunomide, fingolimod and best supportive care compared with Rebif-44, fingolimod and best supportive care), or adding an additional treatment line (for example, teriflunomide, Rebif-44 and fingolimod compared with Rebif-44, fingolimod and best supportive care). The other 2 sequences included a comparison of teriflunomide, Rebif-44 and glatiramer acetate with Rebif-44, glatiramer acetate and best supportive care, which resulted in an ICER of £38,200 per QALY gained, and a comparison of Rebif-44, teriflunomide and best supportive care with Rebif-44, glatiramer acetate and best supportive care, which resulted in an ICER of £28,606 per QALY gained.

3.47 External validation of the model, using the parameters applied to the revised base case, was presented in the manufacturer's additional evidence. The resulting ICERs compared with best supportive care were: Avonex £210,570 per QALY gained, Betaferon £1,915,664 per QALY gained, Rebif-22 £371,954 per QALY gained, Rebif-44 £170,893 per QALY gained, and glatiramer acetate £98,785 per QALY gained. These were higher than those presented in [NICE technology appraisal guidance 32](#), which were £48,085, £52,523, £58,817, £78,556 and £97,690 per QALY gained respectively. If treatment waning was excluded from the model (which was not included in NICE technology appraisal guidance 32), the corresponding ICERs for the manufacturer's base-case model, compared with best supportive care, were lower: Avonex £117,759 per QALY gained, Betaferon £131,825 per QALY gained, Rebif-22 £65,486 per QALY gained, Rebif-44 £79,027 per QALY gained, and glatiramer acetate £46,473 per QALY gained.

The ERG critique of the manufacturer's additional evidence

3.48 The ERG reviewed the additional evidence presented by the manufacturer and commented that the document submitted by the manufacturer largely reflected the amendments and corrections intended to address the Committee's considerations. Furthermore, the ERG noted

that the meta-regression methods used to adjust the MTC for baseline relapse rates were acceptable. The ERG commented that the meta-regression carried out by the manufacturer resulted in a reduction in the effect size of Rebif-44, Betaferon and glatiramer acetate for 3-month SAD and discontinuations. The ERG commented that this was because the trials in the MTC with the largest baseline relapse rates were the placebo-controlled Rebif-44, Betaferon and glatiramer acetate trials. The ERG noted that the adjusted 'all years' MTC had similar results to the 'all years' MTC and base-case (post-2000) MTC but that some of the point estimates favoured teriflunomide more than the base-case (post-2000) MTC.

- 3.49 The ERG reran the sensitivity analyses conducted by the manufacturer for treatment waning, inclusion of non-medical costs and treatment sequencing, and the results were similar to those presented by the manufacturer. The ERG explored the inclusion of some non-medical costs, using a cost midpoint from Karampampa et al. (2012). When these costs were applied, teriflunomide dominated the beta interferons in the probabilistic and deterministic analyses. In addition, teriflunomide dominated glatiramer acetate in the probabilistic analyses, and a deterministic ICER of £2729 per QALY gained was estimated for teriflunomide compared with glatiramer acetate.
- 3.50 The ERG conducted further exploratory analyses to show the key driver in the ICER difference between the ERG's re-estimation of the revised manufacturer's base case (£13,972 per QALY gained) and the ERG's previously preferred scenario (£107,148 per QALY gained), for teriflunomide compared with glatiramer acetate. The ERG noted that the only difference in the parameters applied to these analyses was the MTC (adjusted 'all years' MTC or 'all years' MTC, respectively), and inclusion of treatment waning. The ERG applied the disability progression rate from the 'all years' MTC rather than from the adjusted 'all years' MTC to the manufacturer's revised base case and this increased the ICER from £13,972 to £109,237 per QALY gained for teriflunomide compared with glatiramer acetate. The ERG applied the withdrawal rate from the 'all years' MTC rather than from the adjusted 'all years' MTC to the manufacturers revised base case and this increased the ICER from £13,972 to £22,797 per QALY gained for teriflunomide compared with

glatiramer acetate. The ERG explored the impact of having the same withdrawal rate for glatiramer acetate and teriflunomide in the manufacturer's revised base case and the estimated ICER was £32,971 per QALY gained for teriflunomide compared with glatiramer acetate.

3.51 The ERG noted that the treatment sequencing highlighted the difference in costs and effectiveness when teriflunomide is added to current treatment, rather than replacing an existing therapy. The ERG therefore compared teriflunomide with best supportive care to understand this impact. The ERG explored the impact of including or excluding treatment waning, and including, excluding or applying a midpoint for non-medical costs, the resulting ICERs were:

- including treatment waning:
 - excluding non-medical costs, £64,032 per QALY gained
 - including non-medical costs, £50,743 per QALY gained
 - using a cost midpoint (see section 3.49), £50,602 per QALY gained.
- excluding treatment waning:
 - excluding non-medical costs, £42,243 per QALY gained
 - including non-medical costs, £29,293 per QALY gained
 - using a cost midpoint (see section 3.49), £29,289 per QALY gained.

3.52 The ERG commented on the validation of the manufacturer's model. The ERG noted that the ICERs of the disease-modifying treatments compared with placebo presented by the manufacturer were higher than those in [NICE technology appraisal guidance 32](#). The ERG commented that the manufacturer's model predicted slower progression but a lower health-related quality of life than seen from the UK risk-sharing scheme.

3.53 Full details of all the evidence are in the [manufacturer's submission](#) and the [ERG report](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of teriflunomide, having considered evidence on the nature of active relapsing–remitting multiple sclerosis and the value placed on the benefits of teriflunomide by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

- 4.1 The Committee heard from the clinical specialists and patient experts about the nature of the condition. It was aware that relapsing–remitting multiple sclerosis is a chronic, disabling, neurological condition that, as it progresses, can be life altering and have a substantial negative impact on quality of life and activities of daily living. The patient experts emphasised that people with multiple sclerosis can lose independence and are often not able to continue working. The Committee heard from a patient expert that only 25% of people with multiple sclerosis are employed 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 do not work. The patient experts emphasised the importance of having access to new treatments that could reduce the number of relapses and therefore slow the accumulation of disability. The Committee noted that most current treatments for active relapsing–remitting multiple sclerosis need to be injected and may 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. A patient expert described experiencing 2 or 3 days of feeling very unwell from flu-like symptoms after injecting treatment, followed by 3 days of dreading the next injection, and commented that they had taken time off work because of the side effects of treatment. The Committee heard from the patient experts that some people find it difficult to inject because of the stigma attached with taking an injection. It also heard that because teriflunomide is given orally and has a different side-effect profile than currently available treatments, it would be very beneficial. The Committee understood that any delay in relapse and progression of disability or relief from using injectable treatments would have a positive impact on the lives of people with multiple sclerosis and their families.

- 4.2 The Committee discussed the management of active relapsing–remitting multiple sclerosis and considered the likely position of teriflunomide in the treatment pathway for adults with active relapsing–remitting multiple sclerosis. It heard from the clinical specialists that most patients with active relapsing–remitting multiple sclerosis 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, Extavia] or glatiramer acetate), in line with the Association for British Neurologists' guidelines. The Committee heard from the clinical specialists that in the UK clinical practice treatment varies and that there is no clear treatment pathway. The clinical specialists explained that the choice of whether to take glatiramer acetate or beta interferon, and which beta interferon to take, was a decision made between the clinician and the patient, taking into account the patient's views and thoughts on the route and schedule of administration, the side-effect profile and how the drug is stored. The Committee was aware that beta interferons and glatiramer acetate were not recommended in Beta interferon and glatiramer acetate for the treatment of multiple sclerosis (NICE technology appraisal guidance 32). However, it acknowledged that after this guidance was issued, the Department of Health agreed a risk-sharing scheme with manufacturers through which disease-modifying treatments for multiple sclerosis can be provided to patients in the NHS at a level that the Department of Health considers to be cost effective, and that use of disease-modifying therapies has become firmly established practice in the NHS. The Committee was aware that the role 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. The clinical specialists commented that in clinical practice teriflunomide would be considered as a treatment option in the same way as glatiramer acetate or beta interferons. The Committee understood that teriflunomide would be used in line with the Association for British Neurologists' guidelines, and that it would be stopped if the person's condition converted to secondary progressive multiple sclerosis, or reached EDSS state 7.
- 4.3 The Committee discussed the management of rapidly evolving severe relapsing–remitting multiple sclerosis and highly active

relapsing–remitting multiple sclerosis. It was aware that, in Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (NICE technology appraisal guidance 127), natalizumab is recommended for treating rapidly evolving severe relapsing–remitting multiple sclerosis (defined as 2 or more disabling relapses in 1 year, and 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI). The Committee heard from the clinical specialists that more aggressive disease is difficult to identify in the first 2 years of onset but, for these people, natalizumab would be considered the most appropriate first-line treatment option. The Committee was aware that Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (NICE technology appraisal guidance 254) recommends fingolimod for treating highly active relapsing–remitting multiple sclerosis in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon. The clinical specialists highlighted to the Committee that, because of the lack of treatment options for patients with rapidly evolving severe relapsing–remitting multiple sclerosis and highly active relapsing–remitting multiple sclerosis, teriflunomide may be considered as an option for these patients, but it would not be used routinely.

Clinical effectiveness

- 4.4 The Committee discussed the clinical-effectiveness evidence from the trials. The Committee understood that the marketing authorisation included all people with relapsing–remitting multiple sclerosis, but that the trials included people who had 1 relapse in the last year or 2 in the last 2 years, and therefore were patients with more severe relapsing–remitting multiple sclerosis than the general population with relapsing–remitting multiple sclerosis; that is, they had active disease. It heard from the clinical specialists that the trial populations broadly represented patients who would be offered beta interferon or glatiramer acetate in the UK, in line with the Association of British Neurologists' guidelines. The Committee therefore concluded that the trial populations appropriately represented the decision problem because these would be the people who would receive treatment with disease-modifying treatment in the UK.

- 4.5 The Committee agreed that there was sufficient evidence to conclude that, compared with placebo, teriflunomide statistically significantly reduced annualised relapse rates in both the TEMSO and TOWER trials and the meta-analyses (see [section 3.4](#)), and that the proportion of people who experienced 3-month sustained accumulation of disability (SAD) was reduced with teriflunomide compared with placebo and that this difference was statistically significant in the TEMSO trial and in the meta-analysis (see [section 3.4](#)). The Committee agreed, however, that there was no statistically significant difference between teriflunomide and placebo in 6-month SAD in either of the placebo-controlled trials (see [section 3.4](#)). The Committee concluded that teriflunomide was clinically effective in reducing relapse rates compared with placebo, and that teriflunomide may have a beneficial impact on accumulation of disability compared with placebo.
- 4.6 The Committee discussed the appropriateness of reporting 3-month SAD rather than 6-month SAD. It heard from the clinical specialists that recovery from relapse may continue for up to 12 months, but on average, recovery from the disabling effects of a relapse will be seen within 3 or 4 months. The clinical specialists stated that 6-month SAD is therefore a more robust outcome measure than 3-month SAD for measuring disability progression. The Committee was also aware that sustained disability progression confirmed for 6 months was 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 was aware that most of the multiple sclerosis trials measured 3-month SAD. It acknowledged that this outcome had been considered in previous multiple sclerosis appraisals and that it therefore should be considered in its decision-making. However, the Committee concluded that, although sustained disability progression confirmed for 6 months provides a more robust indication of the treatment effect when measuring disability progression, in light of the lack of 6-month SAD data available, 3-month SAD data should be considered.
- 4.7 The Committee discussed the mixed treatment comparison (MTC) presented by the manufacturer that compared teriflunomide with the beta interferons and glatiramer acetate. It noted that the manufacturer

had presented a base-case MTC, which had excluded trials that recruited patients before the year 2000 ('post-2000'), and one that included all trials ('all years') (see [section 3.6](#)). The Committee acknowledged that trials carried out before the year 2000 were excluded because of changes in diagnostic criteria, which has resulted, in part, in changes in baseline relapse rates over time, but were concerned that important trials were excluded because of the cut-off date, including all trials comparing beta interferons with placebo (see [section 3.29](#)). The Committee agreed that an MTC should include all available evidence and that, in this case, adjusting the MTC for baseline relapse rates would account for any differences in relapse rates between trials. The Committee noted that the results from the adjusted 'all years' MTC, provided in response to consultation, were similar to those from the 'all years' MTC (see [section 3.43](#)). The Committee concluded that the adjusted MTC was the most appropriate and that, based on the MTC, there was no difference in effectiveness between teriflunomide and the beta interferons or glatiramer acetate (see [section 3.43](#)).

- 4.8 The Committee discussed the TENERE trial, which did not show any statistically significant differences in annualised relapse rate between teriflunomide and the active comparator Rebif-44 (interferon beta-1a, 44 micrograms) (see [section 3.5](#)). The Committee heard from the manufacturer that the primary outcome of the trial was time to failure and that the trial was not a non-inferiority or equivalence trial. It had been powered to test the hypothesis that people will stay on an oral drug with a different side-effect profile longer than on an injectable drug. The Committee noted that the TENERE trial was designed to show the benefits of an oral drug and had not been designed to compare the effectiveness of teriflunomide with Rebif. Therefore, the Committee concluded that the effectiveness of teriflunomide compared with Rebif-44 was still uncertain, and that the MTC results did not show a difference in effectiveness.
- 4.9 The Committee discussed the evidence for the effectiveness of teriflunomide in patients with rapidly evolving severe relapsing–remitting multiple sclerosis or highly active relapsing–remitting multiple sclerosis, and the comparisons with natalizumab and fingolimod, respectively. The Committee noted that the manufacturer had stated in its submission that

these were not key comparators for teriflunomide. The Committee noted that the MTC results favoured natalizumab and fingolimod for the outcome annualised relapse rate, and that no difference was found between teriflunomide and the 2 drugs for 3-month SAD. However, the Committee agreed that the MTC results, being based on the whole trial population, did not provide relevant information for the subgroups. The Committee concluded that the indirect comparisons carried out for the subgroups could not be considered reliable because of the small patient numbers and the inadequate methodology used (see [sections 3.10](#) and [3.42](#)). It therefore concluded that the evidence was insufficient to make any conclusions about the clinical effectiveness of teriflunomide compared with natalizumab and fingolimod in the respective subgroups. It noted that the clinical specialists confirmed that teriflunomide would not be routinely used in people with aggressive disease (see [section 4.3](#)). The Committee also noted that no comments to support the use of teriflunomide in these subgroups were received during consultation on the appraisal consultation document. The Committee concluded that the evidence presented by the manufacturer was insufficient to recommend teriflunomide for treating highly active relapsing–remitting multiple sclerosis or rapidly evolving severe relapsing–remitting multiple sclerosis.

- 4.10 The Committee was aware of the adverse effects associated with teriflunomide (see [section 3.11](#)). The Committee discussed the risk of teratogenicity with teriflunomide, and the long 'washout' period (2 years) needed for women to have stopped treatment before trying to conceive. It agreed that this was a particular concern because multiple sclerosis affects women of childbearing age. The Committee recognised, however, that none of the disease-modifying drugs are recommended in pregnancy, and therefore it was a concern for all the multiple sclerosis treatments (although the washout period with teriflunomide is longer). The Committee considered this a notable concern, but concluded that no additional monitoring for teriflunomide had been recommended than that already given for treatment with the disease-modifying therapies and therefore it would not need to be reflected in the modelling for teriflunomide.

Cost effectiveness

- 4.11 The Committee discussed the revised base case provided by the manufacturer, the ERG's critique of the manufacturer's additional analyses, and the comments from patient and professional groups, commentators, patient experts and clinical specialists received in response to the appraisal consultation document. The Committee understood the manufacturer's model to be structurally similar to models used in previous NICE technology appraisals. The Committee agreed that the manufacturer's revised base case reflected the Committee's preferred analyses. That is, it used the ERG's preferred scenario (see [section 3.40](#)), and the following changes:
- the 'all years' MTC adjusted for baseline relapse rates was used to estimate disease progression and withdrawal rates
 - treatment waning (75% treatment effect after 2 years and 50% treatment effect after 5 years) was included, and
 - the results were presented incrementally for all comparators rather than using a blended comparator.
- 4.12 The Committee discussed the external validation presented by the manufacturer in response to the appraisal consultation document. The Committee noted that the incremental cost-effectiveness ratios (ICERs) estimated by the manufacturer's revised model were substantially higher than those in [NICE technology appraisal guidance 32](#) for most of the comparators, and that the manufacturer's model predicted slower disease progression and lower health-related quality of life than the UK risk sharing scheme (see [section 3.52](#)). The Committee noted the considerable uncertainty in the current analyses, and the analyses carried out for NICE technology appraisal guidance 32, and acknowledged that showing close convergence between the previous and present analyses was challenging. However, the Committee concluded that the manufacturer's model was sufficiently valid for decision-making in the current appraisal.
- 4.13 The Committee was aware from the original analyses that disease progression was the main driver of the ICERs; using the ERG's original

preferred analyses, the ICER ranged from £6000 per QALY gained (deterministic, using the base-case MTC [post 2000]) to £107,000 per QALY gained (probabilistic, using the 'all years' MTC) for teriflunomide compared with glatiramer acetate. The Committee concluded that the most appropriate MTC to use was the 'all years' MTC adjusted for baseline relapse rate because it included all available studies and accounted for the differences in baseline relapse rates seen between studies. The Committee noted that this resulted in an ICER of £14,000 per QALY gained for teriflunomide compared with glatiramer acetate (as estimated by the ERG).

- 4.14 The Committee understood that withdrawal rates had a counterintuitive impact on the ICER, in that increasing the withdrawal rate reduced the ICER. The Committee noted from the ERG's exploratory analyses that, when the withdrawal rate from the 'all years' MTC rather than from the 'all years' MTC adjusted for baseline relapse was applied to the ERG's re-estimation of the manufacturers revised base-case analysis, the ICER for teriflunomide compared with glatiramer acetate increased from £14,000 to £23,000 per QALY gained (see [section 3.50](#)). In addition, when it was assumed that the withdrawal rates for glatiramer acetate and teriflunomide were equal, the estimated ICER was £33,000 per QALY gained. The Committee agreed that assuming withdrawal rates were equal was the most conservative approach, but that using the 'all years' MTC adjusted for baseline relapse rate to estimate withdrawal rates was appropriate.
- 4.15 The Committee discussed how the manufacturer's revised base case modelled the natural history of multiple sclerosis. It recognised that the placebo arms of the TEMSO and TOWER trials had been used to model the natural history of disease. The Committee noted that, in response to the consultation, the manufacturer had stated that using data from the placebo arms of the TOWER and TEMSO trials overestimated EDSS regression, especially at higher EDSS states, and that applying rates from the London Ontario data set for the higher EDSS states reduced the ICER. The Committee noted the inherent limitations associated with using the London Ontario data set to model the natural history of disease, namely, that it allowed only for movement to higher EDSS states, and that it reflected a cohort from the 1970s and 1980s. It agreed

that it was appropriate for the model to allow movement to lower as well as to higher EDSS states, that is, to allow for the condition to both improve and get worse, which is in line with what is seen in clinical practice for the lower EDSS states. The Committee also heard from the clinical specialists that relapses are less likely to occur once patients are in higher EDSS states; and people are less likely to move to lower EDSS states. The Committee agreed that using the data from the placebo arms of the TOWER and TEMSO trials was appropriate for modelling disease progression.

- 4.16 The Committee heard from the clinical specialists that the health-related quality of life of people with multiple sclerosis was more closely related to EDSS state than to the clinical form of multiple sclerosis (that is, relapsing–remitting or secondary progressive). The clinical specialists stated that it is difficult to clearly identify when the condition becomes secondary progressive multiple sclerosis, and so it is also difficult to gauge the impact of progressing to secondary progressive multiple sclerosis on health-related quality of life. The Committee noted that, in the revised base case, the manufacturer had used clinical trial data to estimate utility values, where possible. For the higher EDSS states that could not be derived from clinical data, the manufacturer had extrapolated values using the differences in utility between EDSS states seen in Orme et al. (2007). The Committee agreed that this approach was appropriate.
- 4.17 The Committee discussed the disutility values incorporated in the model to reflect caregiver disutility, as in previous multiple sclerosis appraisals, and considered this to be appropriate. The Committee noted that the disutility values for adverse events included in the model were small (see [section 3.15](#)), and acknowledged the comment raised during consultation that a more extensive list of adverse events should be included in the model. The Committee understood that the disutility values did not have a large impact on the ICERs and therefore concluded that it did not need to consider the disutility values in the model further.
- 4.18 The Committee considered the duration of treatment benefit on disease progression, and noted that it remained constant over time in the manufacturer's original base case. That is, there was no option for the

treatment benefit to decrease over time. It recognised that the long-term benefit was largely unknown but that it had a large impact on the outputs of the model. The Committee heard from the clinical specialists that they could not be confident that the treatment effect would not wane. The Committee acknowledged that, in the revised model, the manufacturer had included the assumption that the treatment effect decreased to 75% at 2 years and 50% at 5 years to explore a reduction of the long-term treatment effect. The Committee noted that applying treatment waning increased the ICER for teriflunomide compared with glatiramer acetate (from £10,000 to £13,000 per QALY gained, see [section 3.45](#)). The Committee agreed that it was important to include in the decision-making that the treatment effect could decrease over time but, given the uncertainty of how much the treatment effect would wane, the most plausible ICER was likely to lie between the estimates that included and excluded the modelled treatment waning effect.

4.19 The Committee considered the cost data used in the manufacturer's revised base case. It was concerned that the non-health costs contributed to a high proportion of the costs in the model, and it was unclear what proportion of these costs would include personal social services, and therefore would be appropriately included in the NICE reference case. The Committee acknowledged that the manufacturer had provided scenarios with and without non-health costs (with non-health costs: £13,000 per QALY gained compared with glatiramer acetate; without non-health costs: teriflunomide dominated glatiramer acetate). It recognised that the ERG's critique of the manufacturer's revised base case included a scenario using a cost midpoint, which increased the ICER slightly compared with including all non-health costs (deterministic ICER £3000 per QALY gained). The Committee understood that excluding all non-health costs was a conservative but arguably appropriate approach to adjusting the model's cost inputs to follow NICE's preferred perspective for analyses. The Committee concluded, however, that the most plausible ICER was likely to lie between the ICERs estimated with and without non-health costs, given the uncertainty about how much of the non-health costs from the cited sources were within the NICE reference case.

4.20 The Committee recognised that no specific sequence of disease-

modifying treatments was standard practice in the NHS but that patients with active relapsing–remitting multiple sclerosis often receive more than 1 disease-modifying treatment over time. Therefore the Committee considered it important to explore how sensitive the ICERs were to the inclusion of more than 1 treatment. The Committee understood that teriflunomide may be added to the treatment pathway and, in this situation, the alternative treatment would be best supportive care. The Committee noted that the ERG's exploratory analysis comparing teriflunomide with best supportive care gave ICERs for teriflunomide of between £29,000 and £64,000 per QALY gained, depending on whether treatment waning or non-health costs were included. The Committee noted that these ICERs were lower than the ICERs for the disease-modifying treatments from the risk sharing scheme, when derived from the same model (the revised manufacturer's analysis). The Committee agreed that it was valuable to understand the impact on the ICER of including teriflunomide in a treatment sequence, or as an alternative to best supportive care (to account for adding to the treatment sequence), and agreed that for future technology appraisals in multiple sclerosis, a scenario in which a sequence is explored would be useful. However, the Committee concluded that the analysis of individual drugs (without a sequence) was the basis for decision-making in this appraisal because of:

- the lack of an established common treatment pathway
- the resulting uncertainties related to the modelling of sequencing
- the difficulty with cross-model validation
- the fact that considering treatment sequences formally in its recommendations would go beyond the scope of this appraisal.

4.21 The Committee discussed whether teriflunomide was innovative and noted the comments received during consultation on the appraisal consultation document. It recognised the limitations of the current treatments in terms of their side-effect profile and administration methods, and agreed that an oral treatment, with a different side-effect profile, would be beneficial for people with active relapsing–remitting multiple sclerosis. The Committee discussed whether there were health-related benefits associated with an oral treatment that were not captured

in the modelling. It noted that the manufacturer's economic model assigned different disutilities for treatment-specific adverse events, including injection site reactions and that, therefore, some of the benefits of oral treatment had been captured, but possibly not all. The Committee concluded that teriflunomide was innovative and that additional health-related quality-of-life benefits related to the oral treatment may not have been captured fully.

4.22 The Committee considered the manufacturer's revised base-case results and the ERG's critique of these data, noting that teriflunomide dominated the beta interferons, and that the ICER for teriflunomide compared with glatiramer acetate was £14,000 per QALY gained. The Committee noted that excluding treatment waning reduced the ICER for teriflunomide compared with glatiramer acetate to £10,000 per QALY gained and that, when non-health costs were included, teriflunomide dominated the beta interferons and glatiramer acetate, irrespective of whether waning was included or excluded. The Committee acknowledged that when some non-health costs were included, as modelled by the ERG, the ICER for teriflunomide compared with glatiramer acetate was £3000 per QALY gained and that when withdrawal rates were assumed equal between teriflunomide and glatiramer acetate, as presented by the ERG, the ICER was £33,000 per QALY gained. The Committee concluded that teriflunomide dominated the beta interferons. For the comparison with glatiramer acetate, the Committee noted the varying ICERs from the different analyses and recognised that there were benefits not captured in the QALY, such as the oral administration of teriflunomide. The Committee concluded that, on balance, the most plausible ICER for teriflunomide compared with glatiramer acetate would be below £20,000 per QALY gained.

4.23 The Committee agreed there was insufficient evidence to appraise the cost effectiveness of teriflunomide compared with fingolimod for the highly active relapsing–remitting multiple sclerosis or with natalizumab for the rapidly evolving severe relapsing–remitting multiple sclerosis. The Committee therefore concluded that teriflunomide cannot be recommended for treating highly active relapsing–remitting multiple sclerosis or rapidly evolving severe relapsing–remitting multiple sclerosis. However, the Committee concluded that teriflunomide could be

considered an 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, and who do not have highly active relapsing–remitting multiple sclerosis or rapidly evolving severe relapsing–remitting multiple sclerosis, and only if the manufacturer provides teriflunomide with the discount agreed in the patient access scheme.

Summary of Appraisal Committee's key conclusions

TA303	Appraisal title: Teriflunomide for treating relapsing–remitting multiple sclerosis	Section
Key conclusion		
Teriflunomide 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 <ul style="list-style-type: none"> • they do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis and • the manufacturer provides teriflunomide with the discount agreed in the patient access scheme. 		1.1
Compared with placebo, teriflunomide reduced relapse rates, and may have a beneficial impact on accumulation of disability. Based on a mixed treatment comparison (MTC), there was no difference in effectiveness between teriflunomide and the beta interferons or glatiramer acetate.		4.5, 4.7, 4.8

<p>The evidence was insufficient to make any conclusions about the clinical effectiveness of teriflunomide for the subgroups with highly active relapsing–remitting multiple sclerosis and rapidly evolving severe relapsing–remitting multiple sclerosis compared with natalizumab and fingolimod because the MTC, being based on the whole trial population, did not provide relevant information, and the indirect comparisons could not be considered reliable because of the small patient numbers and inadequate methodology used. Therefore, the Committee could not recommend teriflunomide for treating highly active relapsing–remitting multiple sclerosis and rapidly evolving severe relapsing–remitting multiple sclerosis.</p>		4.9
<p>Based on the revised modelling teriflunomide dominated the beta interferons. For the comparison with glatiramer acetate, the Committee concluded that, when accounting for the benefits associated with the oral administration, which were not captured in the modelling, the most plausible ICER for teriflunomide compared with glatiramer acetate would be below £20,000 per QALY gained.</p>		4.22
Current practice		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>Relapsing–remitting multiple sclerosis is a chronic, disabling, neurological condition that, as it progresses, can be life altering and have a substantial negative impact on quality of life and activities of daily living. Current treatments all need to be injected, and can be associated with unpleasant side effects. The Committee concluded that any delay in relapse and progression of disability or relief from using injectable treatments would have a positive impact on the lives of people with multiple sclerosis and their families.</p>	4.1
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 agreed that, as an oral treatment with a different side-effect profile, teriflunomide offered a step change for treating relapsing–remitting multiple sclerosis, which could have a substantial impact on quality of life for people with relapsing–remitting multiple sclerosis.	4.1, 4.21
What is the position of the treatment in the pathway of care for the condition?	Teriflunomide would be considered for people with active relapsing–remitting multiple sclerosis as an option, in the same way as glatiramer acetate and the beta interferons, and would be used in line with the Association for British Neurologists' guidelines, and would be stopped if the person's condition converted to secondary progressive multiple sclerosis, or reached Expanded Disability Status Scale (EDSS) state 7.	4.2
Adverse reactions	The Committee understood that teriflunomide is associated with diarrhoea, nausea, vomiting, increased levels of alanine aminotransferase, parathesias and dysesthesias, infections and alopecia.	2.2
	The Committee considered that the teratogenicity with teriflunomide, and the long 'washout' period (2 years) needed for women to have stopped treatment before trying to conceive is a notable concern, but concluded that no additional monitoring was recommended for teriflunomide over that already given for treatment with the disease-modifying therapies and therefore it would not need to be reflected in the modelling for teriflunomide.	4.10
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The manufacturer provided evidence from 3 phase III clinical trials (TESMO, TOWER and TENERE), a phase II clinical trial, a meta-analysis, an MTC and an indirect treatment comparison. Two of the phase III clinical trials (TESMO and TOWER) and the phase II clinical trial compared the effectiveness of teriflunomide with placebo and were well conducted.	3.1, 3.4, 3.10
	The Committee agreed that an MTC should include all available evidence and that, in this case, adjusting the MTC for baseline relapse rates would account for any differences in relapse rates between trials.	3.6, 4.7
Relevance to general clinical practice in the NHS	The Committee concluded that the trial populations appropriately represented the decision problem because these would be the people who would receive disease-modifying treatment in the UK.	4.4
Uncertainties generated by the evidence	The Committee was aware that, although a statistically significant improvement in 3-month sustained accumulation of disability (SAD) was seen with teriflunomide, this was not seen for 6-month SAD. The Committee concluded that teriflunomide may have a beneficial impact on accumulation of disability.	4.5, 4.6
	The Committee noted that the TENERE trial was designed to show the benefits of an oral drug and had not been designed to compare the effectiveness of teriflunomide with Rebif. Therefore, the Committee concluded that the effectiveness of teriflunomide compared with Rebif-44 was still uncertain.	4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee agreed there was insufficient evidence to make recommendations for teriflunomide for people with highly active relapsing–remitting multiple sclerosis and rapidly evolving severe relapsing–remitting multiple sclerosis	4.9

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that teriflunomide was clinically effective in reducing relapse rates compared with placebo, and that it may have a beneficial impact on accumulation of disability. It agreed that the TENERE trials and the MTC showed that there was no difference in effectiveness between teriflunomide and the beta interferons or glatiramer acetate.	4.5, 4.7, 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer provided a de novo economic model, which the Committee understood to be structurally similar to models used in previous NICE technology appraisals.	3.32, 4.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee acknowledged that there were still some uncertainties in the economic analyses relating to whether treatment waning would occur, the amount of non-health costs that should be considered, and the fact that the benefits of oral treatment are not captured in the QALY.	4.18, 4.19, 4.21
	The Committee noted the ERG's concern about the external validity of the manufacturer's model, and discussed the external validation presented by the manufacturer in response to the appraisal consultation document. The Committee noted that the incremental cost-effectiveness ratios (ICERs) estimated by the manufacturer's revised model were substantially higher than those in NICE technology appraisal guidance 32 for most of the comparators. The Committee noted the considerable uncertainty in the current analyses, and the analyses carried out for NICE technology appraisal guidance 32, and acknowledged that showing close convergence between the previous and present analyses was challenging. The Committee concluded that the manufacturer's model was sufficiently valid for decision-making in the current appraisal.	4.12

<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 the quality-of-life benefits of an oral treatment were not fully captured in the QALY.</p>	<p>4.1, 4.21</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee was aware that the key drivers of the economic model were the choice of comparator, disease progression, the natural history, the rate of transition to secondary progressive multiple sclerosis, and health-related quality of life associated with more severe health states.</p>	<p>4.13, 3.33</p>

Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that teriflunomide dominated the beta interferons. For the comparison with glatiramer acetate, the Committee noted the varying ICERs from the different analyses but accounting for the benefits not captured in the QALY, such as the oral administration of teriflunomide, the Committee concluded that, on balance, the most plausible ICER for teriflunomide compared with glatiramer acetate would be below £20,000 per QALY gained.	4.22
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer of teriflunomide 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 the discount is commercial in confidence.	2.3
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No potential equality considerations were raised.	

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 active relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that teriflunomide 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 teriflunomide will be available to the NHS with a patient access scheme, which makes teriflunomide 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: supply chain, telephone number 01865 405273, customer.services@genzyme.com.
- 5.4 NICE has developed a costing template and report to estimate the national and local savings and costs associated with implementation to help organisations put this guidance into practice.

6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the [NICE website](#).

Published

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

Under development

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

- Dimethyl fumarate for treating relapsing–remitting multiple sclerosis. NICE technology appraisal. Publication expected January 2014.
- Alemtuzumab for treating relapsing–remitting multiple sclerosis. NICE technology appraisal. Publication expected April 2014.
- Laquinimod for treating relapsing–remitting multiple sclerosis. NICE technology appraisal. Publication expected February 2014.

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review once the update of NICE technology appraisal guidance 32, NICE technology appraisal guidance 127, and NICE technology appraisal guidance 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
January 2014

8 Appraisal Committee members and NICE project team

8.1 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, University of Exeter Medical School

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 Peter Crome

Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

John Dervan

Lay Member

Professor Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Professor Daniel Hochhauser

Consultant in Medical Oncology, UCL Cancer Institute

Dr Neil Iosson

General Practitioner

Anne Joshua

Associate Director of Pharmacy, NHS Direct

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 and Outcomes Research, Merck Sharp & Dohme

Dr Sanjeev Patel

Consultant Physician and 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

8.2 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.

Melinda Goodall

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:

- Fayter D, Spackman E, Epstein D et al., Teriflunomide for treating relapsing forms of multiple sclerosis, July 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were also invited to comment on the draft scope, the ERG report and the appraisal consultation document. 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:

- Genzyme

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
- Biogen

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 teriflunomide by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the appraisal consultation document.

- Dr Waqar Rashid, Consultant and Honorary Clinical Senior Lecturer in Neurology, Brighton and Sussex University Hospitals NHS Trust, nominated by the Multiple Sclerosis Society - clinical specialist
- Professor Neil Scolding, Consultant Neurologist, Bristol, nominated by the Association of British Neurologists - clinical specialist
- Nick Rijke, Director of Policy and Research, the Multiple Sclerosis Society, nominated by the Multiple Sclerosis Society - patient expert
- Joanne Thomson, nominated by the Multiple Sclerosis Trust - 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.

- Genzyme

Changes after publication

This guidance was published in January 2014. Minor changes to the recommendations were made in June 2014 in line with NICE's current wording style, but the starting date relevant for the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 remains unchanged, which required clinical commissioning groups and NHS England to comply with the recommendations in this appraisal within 3 months of January 2014.

About this guidance

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

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

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](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Accreditation

