NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Teriflunomide for the treatment of relapsing forms of multiple sclerosis

This premeeting briefing is a summary of:

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

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

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

Key issues for consideration

- Can the teriflunomide trials (Study 2001, TEMSO, TENERE and TOWER) be considered generalisable to UK patients with relapsing-remitting multiple sclerosis (RRMS) who would be treated with teriflunomide (see section 3.3 and 4.16)?
- Where in the treatment pathway is teriflunomide being considered?
  - Is it appropriate to consider teriflunomide as an alternative to interferons and glatiramer acetate, and not best supportive care? Taking into account the ABN guidelines, and that the inclusion criteria for the clinical trials TEMSO and TOWER stated that people had one relapse within the last year, or 2 relapses within the last 2 years.
  - Should the rapidly evolving severe RRMS (RES) and highly active RRMS (HA) subgroups be considered as target populations for teriflunomide?

Clinical effectiveness

- Which of the manufacturer's MTCs is the most appropriate – the base case analysis, which excluded all studies that recruited patients before 2000, or the 'All Years' analysis?

- Is it appropriate for the manufacturer to focus on the outcome of sustained accumulation of disability (SAD) for at least 3 months, rather than at least 6 months?
- Are the placebo-controlled trials of teriflunomide (Study 2001, TEMSO and TOWER) and the trials included in the manufacturer's mixed treatment comparison (MTC) sufficiently long enough to capture the outcomes of interest in RRMS including relapse rates and disability progression?
- Taking into account the ERGs comments on the TENERE trial, which compared teriflunomide with beta-interferon Rebif 44µg (that it was not adequately powered, not all patients were followed up for 2 years, there were differences in the arms in terms of previous treatments, and that it was not a double blind trial) can the results from this study be considered robust?
- The ERG identified several inconsistencies between the results of the manufacturer's base case MTC and the head-to-head trials for the outcome of SAD at 3 months. Are the results of the MTC for the outcome of SAD at 3 months valid, given that this outcome was identified by the ERG as a key driver in the economic model?

Cost effectiveness

- Is it appropriate for the main comparator in the manufacturer's cost-effectiveness analysis to be a blended comparator of beta-interferons and glatiramer acetate?
- The ERG noted that the results of the manufacturer's base case MTC for the outcome of 3 month SAD suggests that beta-interferon is less effective than placebo and produced more favourable results for teriflunomide compared with Rebif 44µg than was observed in the clinical trial (TENERE). Which source should be used for the relative treatment effect of teriflunomide in terms of SAD at 3 months: the manufacturer's base case MTC, the 'All years' MTC, TENERE trial effectiveness, or assumed the same as Rebif 44ug?
- Should data from the London Ontario dataset, or from the placebo arms of the TEMSO and TOWER trials be used to inform patient population in terms of initial disability, and natural history of disability progression in the model?

- Should direct non-health costs (which may include costs that do not meet the NICE reference case perspective) be included in the manufacturer's model?
- Which is the most appropriate source of health-state utility values in the manufacturer's model?
- Are the ERG's estimates of the conversion probabilities from RRMS to secondary progressive MS in the model more appropriate than the manufacturer's estimates?
- Do the rules for stopping treatment applied in the manufacturer's model reflect clinical practice?

1 Background: clinical need and practice

1.1 Multiple sclerosis (MS) is a chronic disease associated with demyelination of axons in the central nervous system. The course of MS in an individual patient is unpredictable, but may lead to progressive disability and premature death. The underlying cause of MS remains unknown, but is thought to involve interplay between environmental triggers and genetic susceptibility. A close association between inflammation and neurodegeneration may exist at all stages of MS. People with MS commonly experience fatigue, spasticity, bladder dysfunction, pain and cognitive dysfunction. Less common symptoms are depression, bowel dysfunction and paroxysmal (spasm or seizure) symptoms.

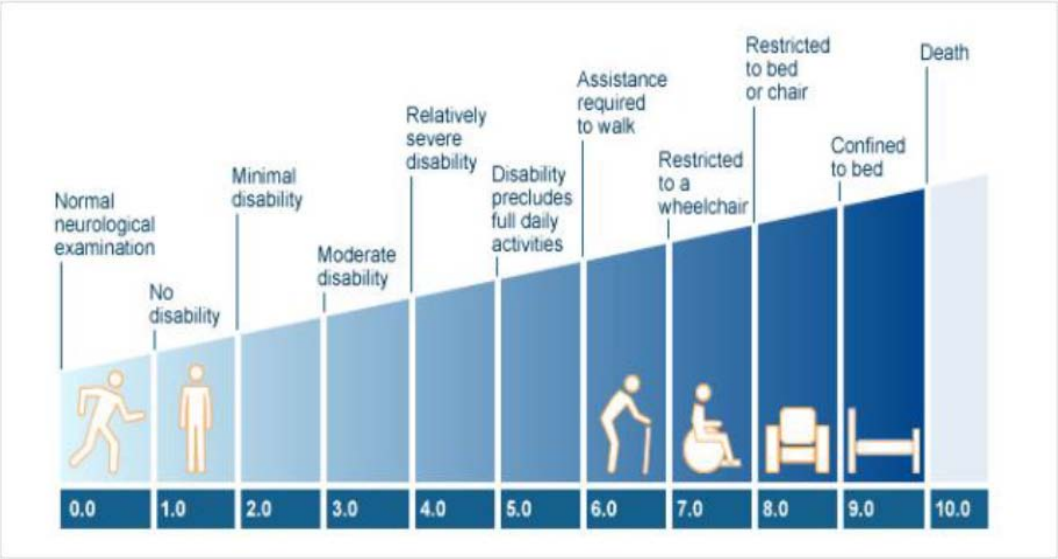
1.2 It has been estimated that 3.5 to 6.6 people per 100,000 are diagnosed each year with MS, and the prevalence is between 100 to 120 per 100,000 in England and Wales. It is a major cause of non-traumatic disability in young adults. The mean age of onset of MS symptoms is between 20-50 years and the highest prevalence is in people aged between 50-64 years. MS predominantly affects women, with an approximate ratio of 3:1.

1.3 In the UK, MS is classified into 3 subtypes: relapsing-remitting, primary progressive and secondary-progressive. Relapsing-remitting MS (RRMS) encompasses people with MS who have periods of remission during their disease course, followed by relapses which may or may not result in underlying disability. A relapse is a clinically evident 'attack' of demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks and then gradually resolving, completely or partially. Relapse rates vary considerably over time and between individuals. There is a general pattern of periods of more frequent relapses followed by long periods of lower rates. The initial relapse rate can be less than one per year and subsequently declines. The assessment of treatments in any individual with relapsed-remitting MS is therefore extremely difficult. Primary progressive MS is the least common form of the disease and is characterised by gradual disability progression from onset, rather than appearing as sudden attacks (relapses). Most people with RRMS develop secondary progressive MS (SPMS), which is characterised by more persistent or gradually increasing disability. Some people with RRMS have more severe disease defined by the number and severity of relapses and by disability caused from the persistent effects of relapse. This clinical subform of RRMS is referred to as highly active RRMS. Highly active RRMS also includes rapidly-evolving severe RRMS which is defined by 2 or more disabling relapses in 1 year and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

1.4 Disability accumulation is a defining feature of RRMS, and can be correlated with the extent of axon injury and the degree of myelin inflammation. The most accepted tool to measure disability in people with relapsed-remitting MS is the 10-point expanded disability status scale (EDSS) depicted in Figure 1. A score of 6 on the EDSS is considered an

important milestone as it represents the onset of walking disability and has implications for treatment (see section 1.5).

Figure 1 The Expanded Disability Status scale (Manufacturers submission page 39)



1.5 There is no cure for MS. Treatment is currently based on disease modifying treatments (DMTs) to reduce the frequency and severity of relapses. Current clinical opinion supports the use of early treatment to prevent accumulation of disability and neurodegeneration. People with relapsed-remitting MS are likely to be started on interferon-beta or glatiramer acetate whichare prescribed according to the criteria described in the Association for British Neurologist (ABN) Guidelines. This guideline states that patients eligible for treatment are adults who can walk (maximum EDSS score of 6.5) with active relapsing disease defined as 2 clinically significant relapses in the previous 2 years. The ABN Guidelines also state that “neurologists may, in certain circumstances where the evidence for efficacy is less secure, also consider advising treatment after discussion with the patient concerning the risks and benefits. For example:

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

Beta interferon and glatiramer acetate are not currently recommended by NICE (technology appraisal guidance 32), but are available in the NHS through a risk-sharing scheme. NICE does however recommend fingolimod and natalizumab for subgroups of RRMS; fingolimod is recommended as an option for treating highly active RRMS and natalizumab is recommended for rapidly evolving, severe RRMS.

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

2 The technology

2.1 Teriflunomide (Aubagio) is an immunomodulatory DMT. It has received a positive Committee for Medicinal Products for Human Use opinion for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS). It is anti-inflammatory; 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 CNS. Teriflunomide is administered as a 14mg oral tablet taken once daily. It can be taken indefinitely, until discontinuation caused by adverse events or treatment failure.

2.2 The draft EPAR lists the following adverse reactions for teriflunomide: diarrhoea, alopecia, nausea and increased alanine aminotransferase. For full details of adverse reactions and contraindications, see the draft EPAR.

2.3 The list price of teriflunomide is £1,037.84 per 28 tablet pack which equates to £13,529 per patient per year. The manufacturer of teriflunomide has agreed a patient access scheme (PAS) with the Department of Health. The scheme is a simple discount scheme, with the discount applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

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

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	• People with relapsing-remitting multiple sclerosis • People with secondary progressive multiple sclerosis who experience relapses • People with progressive relapsing multiple sclerosis	• People with relapsing-remitting multiple sclerosis

3.2 The manufacturer proposed a population different from the decision problem because the anticipated licensed indication refers only to the RRMS population. The treatment pathway outlined by the manufacturer suggested that teriflunomide will be considered in clinical practice as an alternative first-line treatment option to beta-interferon or glatiramer acetate. The ERG agreed that considering only this population and these comparators was appropriate. The ERG noted that highly active MS (HA) and rapidly evolving severe MS (RES) are subtypes of RRMS and that the manufacturer did not consider these as target populations for teriflunomide because these populations would be treated with fingolimod or natalizumab. The manufacturer presented subgroup analyses of patients with HA and RES which the ERG considered to be a reasonable approach.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	Teriflunomide	
Comparators	• Beta-interferon • Glatiramer acetate • Natalizumab (for patients with rapidly evolving severe relapsing remitting MS) • Fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta-interferon	As identified by the final scope issued by NICE we will compare teriflunomide with: • Beta-interferon • Glatiramer acetate The following comparators will be presented if data are available from the phase III trials in these patient groups: • Natalizumab (for patients with rapidly evolving severe relapsing remitting MS) • Fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta-interferon)

Outcomes	• Relapse rate • Severity of relapse • Disability (for example, expanded disability status scale) • Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • Freedom of disease activity • Mortality • Adverse effects of treatment • Health related quality of life	• Relapse rate • Severity of relapse • Disability (for example, expanded disability status scale) • Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • Freedom of disease activity • Mortality • Adverse effects of treatment • Health related quality of life • Resource utilisation: hospitalisation (for relapse or any causes) and emergency medical visits (any causes).

3.3 The manufacturer included all outcomes stated in the decision problem with the addition of a resource use outcome. The ERG noted that the outcomes of severity of relapse and freedom from disease activity listed in the decision problem could not be fully addressed in the manufacturer's submission because they were not pre-specified in the teriflunomide trials. The manufacturer did present data to assess these outcomes; however the ERG commented that the results for these outcomes should be treated with caution. In addition, the ERG noted that quality of life and mortality data were limited to 2-year follow up and supplemented by longer-term extension studies that did not account for the natural history of the disease. The ERG noted that the key outcome of sustained accumulation of disability (SAD) in the manufacturer's submission was defined as an increase from baseline of at least 1.0 point in EDSS score for patients with a baseline EDSS score of less than or equal to 5.5 or at least 0.5 points for patients with baseline EDSS score of greater than 5.5, for at least 3 months. The ERG commented that, although the manufacturer's submission focussed on SAD for at least 3 months (hereafter referred to as 3 month SAD), SAD for at least 6 months would have been preferable because after 3 months there is a strong possibility of improvement to a better EDSS state.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	• The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life. • The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs should be considered from an NHS and Personal Social Services Perspective. • The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. This includes the arrangements within the risk-sharing scheme, which was agreed for the supply of disease modifying treatments for Multiple Sclerosis in the NHS (See Health Service Circular 2002/2004)	• Incremental cost per quality-adjusted life year. • The time horizon considered is lifetime (50 years). • Costs will be considered from an NHS and Personal Social Services perspective. • Costs of beta interferon and glatiramer acetate are obtained from the UK Risk Sharing Scheme. Beta-interferon and glatiramer acetate are the key comparators for teriflunomide. • If data permits comparison with fingolimod or natalizumab, then where patient access schemes are in place and available to the manufacturer these will be taken into account.

3.4 Teriflunomide is being considered by the manufacturer as a first line treatment for RRMS.

4 Clinical-effectiveness evidence

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

- 3 key phase III randomised controlled clinical trials: TEMSO (n=1088, 108 weeks follow-up), TENERE (n=324, 40 to 118 weeks) and TOWER (n=1169, 48 to 154 weeks),

- a phase II proof of concept trial: Study 2001 (n=179, 36 weeks), and
- 2 extension studies: to the proof of concept study (n=147, median 7.1 years follow-up) and to TEMSO (n=742, [redacted]

TEMSO, TOWER, and Study 2001 compared the effectiveness of teriflunomide (7 mg or 14 mg once daily) with placebo. Following completion of the core study for TEMSO and Study 2001, patients 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 µg 3 times a week. Each of the phase III multicentre trials included sites in the UK. The manufacturer also provided a meta-analysis of the placebo-controlled studies (Study 2001, TEMSO, TOWER).

4.2 The primary outcomes were different across the trials. The primary outcome of Study 2001 was combined unique active (new and persisting) lesions per MRI scan, the primary outcome of TEMSO and TOWER was annualised relapse rate (ARR), and the primary outcome of TENERE was time to failure. The trial outcomes presented by the manufacturer included annualised relapse rate, severity of relapse (hospitalisation rate), disability (EDSS score and 3 month SAD), freedom of 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 patients relapse-free, 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.

4.3 The baseline characteristics of the trials are summarised in Table 1. The inclusion criteria of TEMSO, TOWER and Study 2001 specified the number of previous relapses prior to study entry. For TEMSO and TOWER this was at least 1 relapse within the previous year, or at least 2 within the previous 2 years. For Study 2001 this was 1 relapse in the

previous year or 2 within the previous 3 years. The phase III trials included people with an EDSS score between 0 and 5.5, whereas Study 2001 and the extension studies had a range of between 0 and 6.0 (of note, 6.0 represents a significant change in walking ability). There was a greater proportion of people previously treated with a DMT in Study 2001 than the other placebo-controlled trials, and a lower proportion of people with RRMS.

Table 1 Baseline characteristics of Study 2001, TEMSO, TOWER and TENERE

	Study 2001	**TEMSO**	**TOWER**	**TENERE**
n	179	1088	1169	324
Age mean (SD)	39.5	37.9 (8.8)	37.9 (9.3)	36.3 (10.0)
% female	72	72.2	71.1	67.6
% white	NR	98	84	[redacted]
Duration disease since start of symptoms mean (SD)	NR	Median 6.83 yrs.	8.00 (6.72) median 6.25	7.11(7.38)
Duration disease since diagnosis mean (SD)	Approx 5 years	Median 3.5 years	[redacted]	[redacted]
EDSS baseline mean (SD)	Approx 2.25	2.5	2.7 (1.37)	[redacted]
% EDSS $\geq$ 3.5	NR	NR	75.7	[redacted]
Relapses in prior two years, mean (SD)	NR	1 (median in previous 1 yr.)	2.1 (1.2)	[redacted]
% relapsed remitting MS	88	91.5	[redacted]	[redacted]
Previous treatment with DMT	79%	27.0%	[redacted]	[redacted]
% Highly active	NR	1.9%	[redacted]	[redacted]
% Rapidly-evolving severe	NR	6.6%	[redacted]	[redacted]

Taken from the ERG report, table 2 and table 7.

4.4 The manufacturer also presented a mixed treatment comparison (MTC) that compared teriflunomide with each of the treatments in the decision

problem (beta-interferons, glatiramer acetate, natalizumab, fingolimod). The MTC included 30 clinical trials, which recruited patients from 2000 onwards, and included at least 80% of patients with relapsing- remitting MS. A separate 'All Years' analysis was also provided that included studies with recruitment before 2000. The year 2000 was justified by the manufacturer as an appropriate cut-off point because of a reduction in annualised relapse rates at diagnosis in more recent years and changes in diagnostic criteria used in MS trials. After 2000, the McDonald criteria were used which identifies MS earlier than the previously used Poser criteria. The outcomes presented in the MTC included annualised relapse rate, proportion relapse free, 3 month SAD, discontinuation rate and discontinuation rate due to adverse events. The MTC utilised a Bayesian random effects model. The results from the MTC are presented in Table 3 and discussed for each comparator separately in sections 4.9, 4.11, 4.12 and 4.13.

Teriflunomide compared with placebo

4.5 The results from the placebo-controlled trials (Study 2001, TEMSO, TOWER), and a meta-analysis, relate to the 14 mg dose of teriflunomide (summarised in Table 2). These results show that teriflunomide reduced the risk of relapse, increased relapse free periods and reduced disease activity compared with placebo. Teriflunomide was associated with a statistically significant reduction in annualised relapse rate compared with placebo in the TEMSO and TOWER trials, and the meta-analysis. Teriflunomide was associated with a reduction in annualised relapse rate compared with placebo in Study 2001, but this was not statistically significant. A higher proportion of patients were relapse-free at study end or at study reporting with teriflunomide than placebo in Study 2001, TEMSO[redacted] In addition, but not reported in Table 2, in TOWER and TEMSO teriflunomide led to statistically significantly fewer hospitalisations due to relapse than placebo.

4.6 The manufacturer also provided the results of disability outcomes, symptoms, mortality and health related quality of life (Table 2). [redacted] However no statistically significant changes were observed in the other 2 trials. TEMSO showed that statistically significantly fewer people receiving teriflunomide had 3 month SAD than those receiving placebo. TOWER showed lower rates of 3 month SAD with teriflunomide than placebo at both 48 weeks and 132 weeks. The meta-analysis of TEMSO and TOWER (Study 2001 was not included in this analysis) estimated a statistically significantly lower risk of 3 months SAD for teriflunomide compared with placebo (hazard ratio: 0.694, 95% CI: 0.544 to 0.886). However, teriflunomide did not 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). Fatigue and health related quality of life (measured using the SF-36 and EQ-5D) were not statistically significantly different between teriflunomide and placebo in the individual trials, except for minor differences in a single mental health domain.

Table 2. Clinical trial and meta-analysis results, teriflunomide compared with placebo

Outcome		**Treatment**	**Study 2001 (placebo n=61; teri[a] n=57)**	**Study 2001 extension (placebo/ 14mg n=26; 14mg/ 14mg n=40)**	**TEMSO (placebo n=363; teri[a] n=359)**	**TEMSO extension (placebo/14mg n=108; 14mg/14mg n=251)**	**TOWER (placebo n=389; teri[a] n=372)**	**Meta-analysis (random effects)**
Disease activity	Annualised relapse rate	Teri.	0.55 ± 1.12	0.18	0.37 (0.31–0.44) (adjusted)	[redacted]	0.32 (0.27–0.38) (adjusted)	-
		Placebo	0.81 ± 1.22	-	0.54 (0.47–0.62)	-	-	
		Relative risk vs. placebo	0.68 (0.36–1.27)		0.69 (0.58–0.81)		0.64 (0.53–0.77)	0.66 (0.59-0.75)
	Proportion of relapse free patients at study end, or study reporting	Teri.	77%	55.0%	60.6%	[redacted]	[redacted]	-
		Placebo	62% p=0.098	-	49.3% p-value not reported	-	[redacted]	
		Relative risk vs. placebo	2.05 (0.91–4.59)	-	1.54 (1.15–2.06)		[redacted]	[redacted]

Outcome		Treatment	Study 2001 (placebo n=61; teri[a] n=57)	Study 2001 extension (placebo/ 14mg n=26; 14mg/ 14mg n=40)	TEMSO (placebo n=363; teri[a] n=359)	TEMSO extension (placebo/14mg n=108; 14mg/14mg n=251)	TOWER (placebo n=389; teri[a] n=372)	Meta-analysis (random effects)
	Probability of being relapse free	Teri.	-			[redacted]	[redacted]	-
		Placebo				-		
		Hazard ratio vs. placebo					At 132 weeks: 0.63 (0.50–0.79) P<0.0001	
Disability	EDSS score (mean change from baseline)	Teri.	7.4%[b]	0.61±1.11	-	[redacted]	[redacted]	-
		Placebo	21.3%[b]	n/a				
	3 month SAD	Teri.	-	-	20.2% (15.6–24.7)	[redacted]	At 48 weeks: 7.8% At 132 weeks: 15.8%	-
		Placebo			27.3% (22.3–32.3), p=0.03	[redacted]	At 48 weeks: 14.2% At 132 weeks: 21.0%	
		Hazard ratio vs. placebo			0.70 (0.51–0.97)	[redacted][c]	0.69(0.47–1.00), p=0.0442	0.69 (0.54–0.89)
Symptoms	Symptoms (mean change in Fatigue Impact Scale from baseline)	Teri.	-	-	3.8±1.7	[redacted]	1.92	-
		Placebo			4.3±1.7 p=0.83		4.67 (not statistically significant)	

± refers to standard deviation. 95% confidence interval in brackets. All data refer to 14 mg teriflunomide. - : not reported or not applicable; Teri: teriflunomide.SAD: sustained accumulation of disability a) number of people taking the 14mg dose of teriflunomide. b) proportion of patients showing a increase in EDSS compared to baseline at week 36. c) versus patients taking placebo followed by 14 mg teriflunomide. d)People who received 14mg teriflunomide throughout the study and extension. Adapted from tables B6.5.1, B6.6.1, B6.6.2, B6.6.3, B6.6.4 and B6.6.5 in the manufactures submission (pages 119-130,133 and 134)

Teriflunomide compared with interferon β

4.7 The manufacturer provided data from the TENERE study on the clinical effectiveness of teriflunomide 14 mg compared with Rebif 44 µg (IFNβ-1a, 3 times per week). The primary outcome of this trial was time to failure, defined as confirmed relapse or treatment discontinuation. Of those receiving teriflunomide 37.8% reached failure compared with 42.4% in the Rebif 44 µg group. The estimated hazard ratio for failure was 0.861 [redacted]. There were no statistically significant differences between teriflunomide and Rebif 44 µg in the adjusted annualised relapse rate (0.259 vs. 0.216, respectively; p=0.59). The relative risk of relapse was higher with teriflunomide than Rebif 44 µg although this was not statistically significant (RR 1.197, 95% CI 0.623 to 2.299). The proportion of patients who were

relapse free at the end of the study was lower with teriflunomide (76.6%) than Rebif 44 µg (84.6%).

[redacted] In TENERE, the global satisfaction score was used to assess health related quality of life and at week 48 this was statistically significantly higher with teriflunomide than Rebif 44 µg (higher score indicates better satisfaction. 68.818 vs. 60.975, p=0.0162).

4.8 The manufacturer provided results of a mixed treatment comparison (MTC) that included comparison of teriflunomide with the following interferons: Betaferon (INFβ -1b (250 µg)), Avonex (INFβ-1a (30 µg intramuscular) and Rebif 44 µg (subcutaneous). The results of the base case MTC, which are summarised in Table 3, [redacted]

4.9 In UK clinical practice a dose of 22 µg Rebif can be used to treat RRMS (as used in the TENERE study), for patients who cannot tolerate the higher dose of 44 µg. However, no studies were identified using this dose that recruited patients after 2000 for the MTC and therefore the results presented in Table 3 refer to the 44 µg dose. The 22 µg dose of Rebif was considered separately; based on the results of a separate MTC that included studies with patient recruitment prior to 2000. The manufacturer estimated the rates for this dose by calculating the ratio of relative effectiveness of the 22 µg and 44 µg doses (for all outcomes) using all of the data that were available (including pre 2000 recruitment). This ratio was then used to calculate the effectiveness of the 22 µg dose from the results for the 44 µg dose for the studies that recruited after the year 2000. It was estimated that 22 µg Rebif [redacted] the risk of 3 month SAD compared with placebo [redacted] and that

teriflunomide was associated with [redacted] all-cause discontinuations than 22 µg Rebif [redacted]

Table 3 Mixed treatment comparison with teriflunomide (base case and 'All Years' analyses)

Comparator	ARR (rate ratio) (95% Credible interval [CrI]) >1 favours comparator	Proportion relapse free (odds ratio) >1 favours teriflunomide	3 month SAD (hazard ratio) >1 favours comparator	Discontinuation (odds ratio) >1 favours comparator	Discontinuation due to AE (odds ratio) >1 favours comparator
Base case (post-2000) results					
Placebo	0.67 (0.57–0.77)	[redacted]	0.71 (0.53–0.92)	[redacted]	[redacted])
Betaferon	0.98 (0.73–1.31)	[redacted]	0.58 (0.30–1.12)	[redacted]	[redacted]
Avonex	0.86 (0.69–1.05)	[redacted]	0.77 (0.50–1.24)	[redacted]	[redacted]
Rebif 44µg	1.06 (0.84–1.35)	[redacted]	0.90 (0.54–1.45)	[redacted]	[redacted]
GA (20 mg)	1.05 (0.83–1.31)	[redacted]	0.76 (0.45–1.30)	[redacted]	[redacted]
Fingolimod (0.5 mg)	1.45 (1.17–1.80)	[redacted]	0.95 (0.64–1.35)	[redacted]	[redacted]
Natalizumab (300 mg)	2.12 (1.63–2.75)	[redacted]	1.22 (0.77–1.94)	[redacted]	[redacted]
'All Years' results					
Placebo	[redacted]	Not reported	[redacted]	Not reported	[redacted]
Betaferon	[redacted]		[redacted]		[redacted]
Avonex	[redacted]		[redacted]		[redacted]
Rebif 44µg	[redacted]		[redacted]		[redacted]
GA (20 mg)	[redacted]		[redacted]		[redacted]
Fingolimod (0.5 mg)	[redacted]		[redacted]		[redacted]
Natalizumab (300 mg)	[redacted]		[redacted]		[redacted]

Taken from tables B6.7.10, B6.7.13, B6.7.16, B6.7.19 and B6.7.22 (pages 175-181 of the manufacturer's submission) and tables 17-19 of the ERG report (pages 54-57) . GA: Glatiramer acetate; ARR: annualised relapse rate; SAD: sustained accumulation of disability over 3 months; AE: adverse events.

Teriflunomide compared with glatiramer acetate

4.10 Based on the MTC, teriflunomide was associated with a [redacted] probability (odds) of all-cause discontinuation compared with glatiramer acetate. However, [redacted] differences in [redacted] reported between the 2 treatments (Table 3).

Teriflunomide compared with Fingolimod

4.11 Based on the MTC, teriflunomide was associated with a statistically significantly higher rate of annualised relapse compared with fingolimod. [redacted] reported between the 2 treatments (Table 3).

Teriflunomide compared with Natalizumab

4.12 Based on the MTC, teriflunomide was associated with a statistically significantly higher rate of annualised relapse compared with natalizumab. [redacted] reported between the 2 treatments (Table 3).

Highly active and rapidly evolving severe disease

4.13 The manufacturer conducted 2 separate indirect comparisons of teriflunomide for the subgroups of patients with HA and RES disease in TEMSO. For the HA subgroup the relative risks for annualised relapse rate and 3 month SAD were in favour of [redacted] compared with [redacted] For the RES subgroup, the relative risk for annual relapse rate was in favour of [redacted] compared with [redacted] the relative risk for 3 month SAD favoured [redacted] The 95% confidence intervals were not provided for these indirect treatment comparisons.

Table 4 Results of direct and indirect comparisons for highly active disease and rapidly evolving disease subgroups

	Data source	Treatment	ARR (95% CI)	Relapse free	3 month SAD	Discont.	Discont. due to AE
Highly active	TEMSO	Placebo (n=10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

disease		Teriflunomide (n=11)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Teriflunomide vs. placebo (RR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Fingolimod EPAR	Fingolimod vs. placebo (RR)	0.57 (0.28–1.16)	n/a	0.77 (0.31–1.921)	n/a	n/a
	MS	Teriflunomide vs. fingolimod (RR)	[redacted]	n/a	[redacted]	n/a	n/a
Rapidly-evolving severe disease	TEMSO	Placebo (n=39)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Teriflunomide (n=33)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Teriflunomide vs. placebo (RR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NICE sub. (Natalizumab)	Natalizumab vs. placebo (RR)	0.81 (0.70–0.88)	n/a	0.47 (0.24–0.93)	n/a	n/a
	MS	Teriflunomide vs. natalizumab (RR)	[redacted]	n/a	[redacted]	n/a	n/a

RR: relative risk; Discont: discontinuation; Sub: submission; MS: Manufacturers submission. Adapted from tables B6.7.11, B6.7.12, B6.7.14, B6.7.15, B6.7.17, B6.7.18, B6.7.20, B6.7.21, B6.7.23, B6.7.24. of the manufacturers submission (pages175-182)

Adverse events

4.14 The manufacturer states that almost all patients treated with teriflunomide reported at least one treatment emergent adverse event. However for the majority of events, incidence was similar to placebo and were [redacted] as summarised in Table 5. Rates of all-cause discontinuation, however, were higher with teriflunomide than placebo in all of the trials. Rates of discontinuation due to adverse events were higher for teriflunomide compared with placebo, [redacted]. The manufacturer's meta-analysis [redacted] of discontinuations because of adverse events, [redacted] all-cause discontinuations, for teriflunomide compared with placebo. The following adverse events were stated by the manufacturer to be of note: diarrhea, nausea, vomiting, liver function, parathesias and dysaethesias, infections and alopecia.

Table 5 Adverse events in all of the trials

	TEMSO Teriflunomide vs. placebo	**TOWER** Teriflunomide vs. placebo	**Study 2001**	**Meta-analysis**	**Study 2001 extension**	**TEMSO extension**	**TENERE** Teriflunomide vs. Rebif 44µg
Adverse events	87.5% vs. 90.8%	86.3% vs. 83.1%	NS	Not done	100%	[redacted]	92.7% vs. 96.0%
Serious adverse events	12.8% vs. 15.9%	11.9% vs. 12.2%	NS	Not done	28.8%	[redacted]	5.5% vs. 6.9%
All-cause disc. rates	26.5% (terif.)	33.9% vs. 32.1%	21.0% vs. 7.0%	[redacted]	45.4%	[redacted]	19.8% vs. 28.8%
Disc. due to adverse events	10.9% vs. 8.1%	15.6% vs. 6.7%	14.2% vs. 7.0%	[redacted]	19.7%	[redacted]	10.9% vs. 21.8%
Mortality	0	2 teriflunomide neither related to drug	0	Not done	1 death (underlying disease and concomitant medications may have been contributory)	[redacted]	No deaths occurred

Adapted from tables 11 and 12 in the ERG report (page 46). Teriflunomide values are stated first. Disc: discontinuation

Evidence review group comments

4.15 The Evidence Review Group (ERG) concluded that overall the searches for the systematic literature review were appropriate and well documented. However, the ERG noted that there was a protocol of a Cochrane systematic review of teriflunomide missing and that the search strategy could potentially have missed further useful studies, although this was unlikely.

Placebo-controlled trials and meta-analysis

4.16 The ERG considered the generalisability of the placebo-controlled clinical trials to UK clinical practice. It noted that although the majority of the patients in the trials had RRMS (at least 87%), the trials also included people with primary progressive MS and SPMS. They noted that Study 2001 used the Poser rather than McDonald criteria to diagnose patients with MS, and stated that the McDonald criteria were more appropriate and generalisable to current clinical practice. The ERG noted that baseline

EDSS scores and relapse rates were lower in the TEMSO, TOWER and Study 2001 trials than in the UK risk sharing scheme. The ERG commented that the trial populations may be more reflective of a treatment naïve population than was studied in the initial period of the risk sharing scheme. However, it concluded that overall the differences were not large and that the trial populations can be considered generalisable to the UK population.

4.17 The ERG commented that all placebo-controlled clinical trials were of short duration considering the lifelong duration of MS 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 also noted that the European Medical Association (EMA) 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.

4.18 The ERG noted that the TEMSO and TOWER trials reported SAD for at least 3 months and that the EMA recommends 6-month comparative SAD data. The ERG commented that 6 month SAD would be preferable to 3 month SAD because there is a strong possibility of improvement to a better EDSS state at 3 months, and that benefits observed at 3 months may not be sustained over a longer period. In addition, improvements can be seen after 3 month SAD because the disability may not be permanent. 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). They ERG also noted that teriflunomide was not associated with a statistically significant reduction in SAD for at least 6 months compared with placebo in TEMSO or in TOWER, and that meta-analysis of 6 month SAD was not provided by the manufacturer.

4.19 The ERG reviewed the meta-analyses of the placebo-controlled trials that were presented by the manufacturer. The ERG commented that a random effects model, chosen by the manufacturer, 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 2001and the Phase III trials TEMSO and TOWER. The ERG noted that a higher proportion of patients in Study 2001 received previous disease-modifying treatments compared with TEMSO and TOWER. It also noted that Study 2001, as a proof of concept study, was small (61 patients per treatment arm) and study duration was just 36 weeks so relapse rates may not have been robust. Furthermore, it noted that EDSS scores were higher and more patients discontinued treatment in the teriflunomide arm of Study 2001. The ERG stated that these differences suggested that pooling the results of Study 2001 with TOWER and TEMSO was subject to clinical heterogeneity, which could result in statistical heterogeneity. 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 analyses for other outcomes because of its short duration and differences between the arms in previous treatment.

TENERE trial

4.20 The ERG noted that the TENERE trial may not have been adequately powered to detect statistically significant differences in all investigated outcomes.

[redacted]. The ERG commented that because TENERE was not a double-blind trial, it was likely to have biased the evaluation of the primary outcome in favour of teriflunomide (which relies on patient-reported symptoms). The ERG also noted that there were some differences between the treatment arms, in the proportion of patients [redacted] ([redacted] of the Rebif 44µg

treatment group versus [redacted] in the teriflunomide arm) and commented that this makes the results of the trial difficult to interpret.

Mixed treatment comparison

4.21 The ERG noted that the MTC included all of the relevant comparators. They stated that only one potentially relevant trial was missed, but that it would probably not have had a major impact on the estimates of the relative effectiveness of teriflunomide. Overall the ERG concluded that the MTC was inclusive with very few trials omitted.

4.22 The ERG stated that the methods of the MTC were appropriate, except that neither a formal assessment of consistency (in terms of any differences with the results reported in the direct head-to-head studies) nor an assessment of model fit using residual deviance were reported. Informal checks for consistency by the ERG did not identify major problems except the comparison of Betaferon with placebo (3 month SAD HRs of 1.21 in the MTC compared with 0.68 in the TENERE study) and to a lesser extent the comparison of teriflunomide with Rebif 44µg, generated by the smaller base case network for 3 month SAD. 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 the base case analysis). The ERG 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 for 3 month SAD was a key driver in the economic model and therefore the MTC results for this outcome are very important.

4.23 The ERG's one major criticism of the manufacturer's MTC was that pre-2000 trials were excluded in the base case analysis. It noted that one of the reasons stated for this cut off was the change in diagnostic criteria in 2000 from Poser to McDonald. It also noted that the McDonald criteria generally identify patients much earlier in the disease course (with less frequent or severe symptoms) and that a change in diagnostic criteria may

have a considerable impact on the baseline disease activity, in terms of relapse rates, of the patient population being studied. However, the ERG noted that the MTC included 5 studies that had used the earlier Poser criteria. The ERG suggested in a clarification request that the manufacturer should have conducted 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. Similarly, the ERG suggested that additional analyses adjusting for other baseline covariates, including disease duration, EDSS and previous DMT use should have been provided by the manufacturer. However, in response to clarification the manufacturer commented that it was unable to provide these analyses in the timeframe allowed. The ERG noted that the impact of the 2000 cut-off date was that all but one of the placebo controlled trials of beta-interferons and glatiramer acetate were excluded. They commented that whilst the manufacturer's concerns regarding inclusion of 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.

4.24 The ERG reviewed the trials that were included within the MTC and noted that some had a short duration, in both the base case and 'All Years' networks. For example, the network for the outcome of annualised relapse rate included 11 trials, and 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 MS relapse or confirmed progression associated with MS relapse. However, the ERG did not re-run the MTC analyses after excluding these trials of shorter duration. The ERG commented that it was unclear what impact this may have, especially considering outcomes such as relapse and SAD.

Subgroups

4.25 The ERG reviewed the clinical effectiveness evidence provided for the highly active (HA) and rapidly-evolving severe (RES) subgroups. The ERG commented that the results were of limited value because, [redacted] the subgroup analyses indicated that [redacted]

Adverse events

4.26 The ERG noted that the manufacturer's submission did not include a synthesis of adverse effects data that could be readily checked against supporting tables. Furthermore, they noted that the relatively short duration of the placebo-controlled trials limits the assessment of any differences in mortality and less frequently reported adverse events. The ERG noted that meta-analysis of the 3 placebo-controlled trials showed that patients were [redacted] to discontinue treatment because of adverse events compared with placebo. They commented further that although a [redacted] number of patients in the Rebif 44µg arm in TENERE, discontinued treatment because of adverse events, this needs to be interpreted in the light of a [redacted]. The ERG commented that the impact of this difference is unknown.

5 Comments from other consultees

5.1 The professional organisations stated that treatment of RRMS includes 3 categories: treating relapses, treating symptoms and disease modifying treatments. The patient organisations commented on the limitations of the currently available treatments, stating that people with MS sometimes do not start or continue treatment with DMTs because of the side effects, or anxiety about injections. The professional organisations stated that it was anticipated teriflunomide would be positioned as first line treatment

alongside beta-interferon and glatiramer acetate as efficacy and safety profiles were comparable.

5.2 Professional and patient organisation statements clarified that there are no other oral first line DMTs. Patient organisations stated that the vast majority (95%) of people with MS would prefer to oral treatment. They commented that for people with MS their symptoms, such as tremors and numbness in the hands, could make taking an injection difficult. Furthermore they described the pain and stress associated with injecting as well as the inconvenience of taking needles on holidays, or business trips. The patient organisations highlighted the significant impact MS has on patients, their families and carers, noting that MS is often diagnosed at an age when people are developing careers, starting families and taking on financial obligations. They also stated that relapses have a profound impact on ability to work, daily activities, social life and relationships.

5.3 Patient organisations stated that they expect teriflunomide to reduce relapses, reduce disability progression, reduce administration of steroids and hospital admission, and improve quality of life and symptom control. Patient organisations emphasised that teriflunomide's oral route of administration was a particular benefit to patients especially for people who have difficulty with self-injection. They recognised the side effects of teriflunomide are gastrointestinal symptoms, thinning of hair, raised liver enzymes, skin rashes, weight loss, infections and hypertension.

5.4 A professional organisation stated that teriflunomide is a metabolite of leflunomide which has been an established treatment for rheumatoid arthritis for more than a decade. Leflunomide can cause interstitial lung disease, lung fibrosis and liver failure and therefore regular monitoring for these may be needed.

5.5 Professional organisations stated that teriflunomide would offer an additional DMT for patients, but may not increase the number of patients receiving therapy overall. They commented that the monitoring

requirements would not be more extensive than those for currently available treatments.

6 Cost-effectiveness evidence

6.1 The manufacturer provided a de novo model to estimate the cost effectiveness of teriflunomide. In addition, the manufacturer conducted a systematic literature review that identified two cost effectiveness studies for RRMS, although neither included teriflunomide. These were used to inform the manufacturer's model.

6.2 The manufacturer submitted a multi-state Markov model (Figure 2). The health states in the model were defined by disability level (EDSS scores 0-9) and patients with RRMS can enter the model in states 0-7. In each cycle, patients can remain in the same state, progress to a worse state (patients cannot regress to a better state), transfer to a secondary progressive MS (SPMS) health state, or die. Health states for SPMS were included because this represents the clinical progression of RRMS. It was assumed that when progressing from RRMS to an SPMS state the patient's disease would also progress by 1 EDSS state. In addition, in each cycle patients can withdraw from treatment, discontinue treatment after reaching the EDSS limit for which a DMT is allowed (EDSS 6), or experience relapse and adverse events. The probability of death was dependent on the EDSS state, age and ratio of females to males. The transition probabilities, discontinuation rates, relapse rates, and adverse event rates throughout the model were based on trial data, or taken from the literature, as summarised in **Error! Reference source not found.**. Treatment effects on disability and relapse were assumed to be constant over time. In the base case, patients discontinued treatment if they converted from the RRMS to SPMS states or progressed to an EDSS state greater than 6. In the manufacturer's sensitivity analyses, treatment could be continued in SPMS but the treatment effect was reduced by 50% when patients converted from RRMS to SPMS. 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 one year, and the time horizon was a lifetime time horizon, assumed to be 50 years with a mean starting age of 38 years (based on the UK risk sharing scheme cohort). The manufacturer stated that the analyses used an NHS and PSS perspective and applied a 3.5% discount rate on costs and health effects.

Figure 2 Schematic of the manufacturer's model

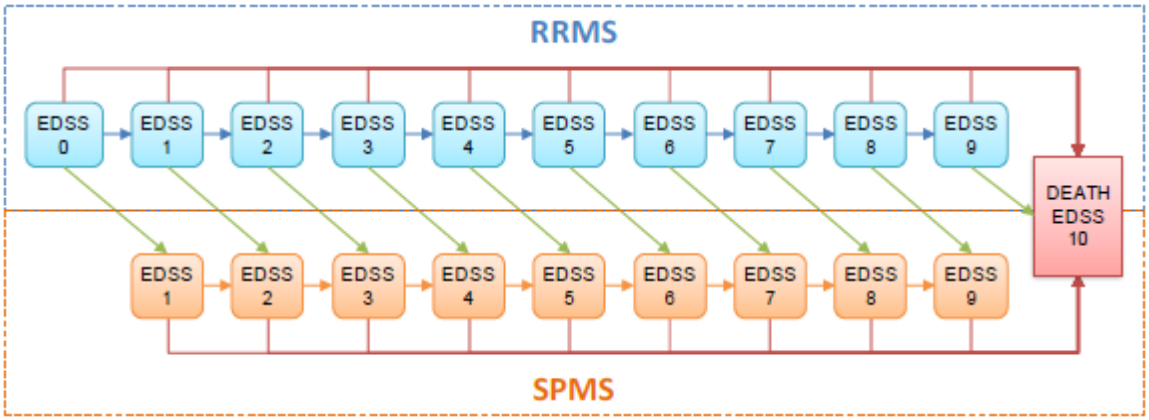


Table 6 Source of the manufacturer's model inputs

Model input	Source (in base case)	Source (sensitivity analyses)
Demographic profile of RRMS patients entering the model (EDSS score, age, female to male ratio)	• UK risk sharing scheme (Pickin et al. 2009)	• TOWER and TEMSO studies
Natural disease progression (transition between EDSS states, conversion from RRMS to SPMS)	• Real world longitudinal observational disability progression data from the London Ontario data set (1989) for most values • Placebo arms of TOWER and TEMSO used for transition from EDSS 0	• n/a
Disease progression (treatment effect) (transition between EDSS states, conversion from RRMS to SPMS)	• Adjusted the natural history transition matrix by the relative treatment effect (3-month SAD) versus placebo derived from the manufacturer's MTC • No treatment effect applied to RRMS to SPMS conversion	• 'All years' MTC

	rates (conversion rates dependent on EDSS states)	
Relapses Relapse rate and severity within each EDSS state (modelled as relapses leading to hospitalisation, or not leading to hospitalisation)	• Held et al. 2005 (relapse rate per year since diagnosis) and Orme et al 2007 UK MS survey (applied to Held et al. to estimate the annual relapse rate for each EDSS state) • Dee at el. 2012 used to estimate the proportion of relapses that lead to hospitalisation	• Patzold et al 1982 and Orme et al 2007 • Proportion of relapses that lead to hospitalisation from placebo arms of TEMSO and TOWER

Relapses (treatment effect)	• MTC used to estimate annualised relapse rates
	• Hospitalisation due to relapse (data applied to base rate):
	  • Teriflunomide: TEMSO
	  • Rebif 44 µg and fingolimod: data from individual trials
	  • Betaferon, Rebif 22 µg, Avonex, glatiramer acetate: assumed same as Rebif 44 µg
	  • Natalizumab: assumed same as fingolimod
		• 'All years' MTC used to estimate annualised relapse rates

Discontinuation/withdrawal rates (all cause, for all treatments)	• Base case MTC • For teriflunomide, manufacturer estimated average withdrawal rates from TENERE, TEMSO, TOWER and Study 2001 trial, and combined this with the MTC data	• 'All years' MTC
Mortality (per EDSS state, irrespective of whether its RRMS or SPMS)	• Used the all-cause mortality rates of the UK general population (England and Wales life tables 2008-2010) and applied a relative increase per EDSS state. EDSS 0 is not associated with an increased mortality risk. • Mortality rate increase with EDSS state estimated from Pokorski et al. 1997	• n/a
Adverse events	• MTC data (rather than using the MTC base case, used all years MTC)	• Adverse event probability in all years equal to probability for

	• Captured AEs that had a greater than or equal to 4% difference in occurrence compared with placebo	year 1

6.3 The manufacturer's base case analyses compared teriflunomide with a blended comparator of Rebif 22 µg, Rebif 44µg, Avonex, Betaferon and glatiramer acetate. The blended comparator was calculated as the weighted average of the clinical efficacy, costs 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 µg, Rebif 44µg, Avonex, Betaferon and aggregated Rebif. The manufacturer also considered treatment sequencing in scenario analyses (see 6.9 and 6.10).The manufacturer provided separate analyses of teriflunomide compared with fingolimod and natalizumab for the RRMS and the RES and HA subgroups.

6.4 The manufacturer's model applied utility values to each of the EDSS states (Table 7). 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. [redacted] The utility values in the manufacturer's model were estimated from Orme et al (2007) which was a UK survey of health related quality of life in (EQ-5D) in people with MS. Of note, EDSS states 8 and 9 had negative utility values indicating a state worse than death. Disutilities were applied for relapse, caregiving and adverse events. The disutility for relapse was estimated from Orme et al. 2007, and a US study (Prosser et al 2003) was used to estimate the disutility for relapse leading to 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). Disutility values were applied for each

adverse event, as summarised in Table 7, which were taken from the published literature. These values refer to the annual disutility of each event. However, the duration of each event was also accounted for to calculate the annual disutility, and was treatment specific.. The adverse events included nausea, diarrhoea, hair thinning, fatigue, headache, immediate post-injection systemic reactions, arthralgia and influenza like symptoms.

Table 7 Utility values (applied per annual cycle) in the manufacturer's model

State	**Expanded disability status scale (EDSS) score**									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Relapsed remitting multiple sclerosis	0.870	0.799	0.705	0.574	0.610	0.518	0.460	0.297	−0.049	−0.195
Secondary progressive multiple sclerosis	0.045 less than relapsed remitting multiple sclerosis									
Caregiver disutility	0.000	−0.001	−0.003	−0.009	−0.009	−0.020	−0.027	−0.053	−0.107	−0.140
Relapse disutility (without hospitalisation)	−0.0089									
Relapse disutility (with hospitalisation)	−0.0297									
Nausea disutility	−0.0001 (teriflunomide)									
Diarrhoea disutility	−0.0004 (teriflunomide, fingolimod)									
Hair thinning disutility	−0.0070 (teriflunomide)									
Fatigue disutility	−0.0004 (natalizumab)									
Arthralgia disutility	−0.0034 (natalizumab)									
Headache disutility	−0.0002 (natalizumab, Avonex, Rebif)									
Injection site reaction disutility	−0.0000 (glatiramer acetate, Betaferon, Rebif)									
Influenza-like symptoms disutility	−0.0005 (glatiramer acetate, Avonex, Betaferon, Rebif)									

Adapted from tables B7.4.6 and B7.4.7 of the manufacturers submission

6.5 The costs applied in the manufacturer's model are summarised in Table 8**Error! Reference source not found.** and Table 9. The manufacturer's model used NHS reference costs and the payment by results (PbR) tariff

to estimate the costs of administration, monitoring and adverse events 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, and the cost associated with relapse from Dee at al 2012. The resource use and costs applied in the model were validated by the manufacturer's clinical experts. Fingolimod is associated with a simple discount through a patient access scheme agreed with the Department of Health. However, the magnitude of this discount was not available to the manufacturer and therefore has not been applied in the base case analysis (but was explored in sensitivity analysis, using a range of discounts).

Table 8 Annual costs associated with technologies in the manufacturer's model

	Tech. cost	Admin. cost (year 1)	Admin. cost (year 2+)	Monitoring cost (year 1)	Monitoring cost (year 2+)	Total (year 1)	Total (year 2+)
Teriflunomide (including PAS)	[redacted]	0	0	407.12	368.24	[redacted]	[redacted]
44µg Rebif	8,942	174	0	355.28	346.64	9,471.28	9,288.64
22µg Rebif	7,513	174	0	355.28	346.64	8,042.28	7,859.64
Avonex	8,502	174	0	355.28	346.64	9,031.28	8,848.64
Betaferon	7,259	174	0	355.28	346.64	7,788.28	7,605.64
Glatiramer acetate	5,823	174	0	338.00	338.00	6,335.00	6,161.00
Fingolimod	19,110	474	0	641.74	346.64	20,225.74	19,456.64
Natalizumab	14,690	6162	6162	493.46	493.46	21,345.46	21,795.26
Blended comparator	7,721	174	0	351.22	344.61	8,246.30	8,065.69

Tech: Technology; Admin: administration. Taken from Table B7.5.8 of the manufacturers submission (page 296)

Table 9 Health state costs (applies to RRMS and SPMS, Tyas et al) included in the manufacturer's model

EDSS health state	Direct medical costs (£)	Other direct non-medical costs (£)	Total (£)
0	336.19	5334.58	5670.77
1	200.23	5779.54	5979.77
2	399.23	6734.96	7134.19
3	1315.10	9565.40	10880.51

4	1294.09	6461.81	7755.90
5	2056.70	9488.77	11545.48
6	3025.73	9811.37	12837.10
7	8595.14	15761.47	24356.62
8	13806.12	20810.53	34616.65
9	19704.31	12914.96	32619.28
10	0	0	0

6.6 All cost effectiveness results presented here include the patient access scheme discount for teriflunomide. The base case results are presented in Table 10. Teriflunomide dominated the blended comparator for both the deterministic and probabilistic analyses, resulting in more QALYs and lower costs. The cost-effectiveness acceptability curve provided by the manufacturer showed a 63% probability of teriflunomide being cost effective at a £20,000 per QALY threshold.

Table 10 Manufacturer's base case results (teriflunomide vs. blended comparator)

Analysis		Total costs	Difference in costs	Total QALYs	Difference in QALYs	ICER
Probabilistic base case	Teriflunomide	[redacted]	−5491	[redacted]	0.201	Teriflunomide dominates
	Blended comparator	[redacted]		[redacted]		
Deterministic base case	Teriflunomide	[redacted]	−6724	[redacted]	0.288	Teriflunomide dominates
	Blended comparator	[redacted]		[redacted]		

Adapted from table 2 and 4 of the manufacturers patient access scheme submission

6.7 The manufacturer conducted one way sensitivity analyses which showed that the cost effectiveness of teriflunomide was most sensitive to the hazard ratio for disability progression (for the blended comparator and teriflunomide), the blended comparator withdrawal rate, disease costs and annual relapse rates (for teriflunomide and the blended comparator). For each of the analyses teriflunomide continued to dominate the blended comparator, except when the hazard ratios for disability progression were varied. When applying the lower 95% confidence interval for the blended comparator disability progression hazard ratio, teriflunomide was

dominated by the blended comparator (resulting in higher costs and lower QALYs). When applying the upper 95% confidence interval for the teriflunomide disability progression hazard ratio, the ICER for teriflunomide compared with the blended comparator was £20,613 per QALY gained.

6.8 The manufacturer conducted scenario analysis that explored treatment sequencing. The sequences explored (Table 11) were based on clinical opinion. As part of these analyses the manufacturer applied 2 PAS prices for finglolimod (£11,000 and £13,000), as well as the list price. Teriflunomide dominated the blended comparator for in all scenarios, irrespective of the size of PAS discount for finglolimod.

Table 11 Treatment sequencing scenarios

	Intervention sequence			Comparator sequence		
Scenario	1st	2nd	3rd	1st	2nd	3rd
Base case	Teriflunomide	BSC	BSC	Blended comparator	BSC	BSC
1	Teriflunomide	Fingolimod	BSC	Blended comparator	Fingolimod	BSC
2	Teriflunomide	Natalizumab	BSC	Blended comparator	Natalizumab	BSC
3	Teriflunomide	Blended comparator	Fingolimod	Blended comparator	Blended comparator	Fingolimod
4	Teriflunomide	Blended comparator	Natalizumab	Blended comparator	Blended comparator	Natalizumab

6.9 The manufacturer conducted a number of additional scenario analyses. Teriflunomide dominated when compared with the blended comparator for all scenarios. The following were investigated:

- Clinical data sourced from all-years, ≥80% RRMS MTC
  - inclusive of all studies
- Clinical data sourced from all-years, ≥80% RRMS MTC excluding a study by Bornstein et al. of glatiramer acetate compared with placebo
  - Bornstein was excluded becasue it did not use EDSS to measure disability progression

- Natural history costs from Karampampa, 2012
  - The costs from Karampampa are lower than the base case for EDSS states 0-3, but higher for the more severe EDSS states.
- Relapse costs from Tyas, et al., 2007
  - Using the values from Tyas means the costs for relapse are the same irrespective of hospitalisation.
- Baseline EDSS utility score from TEMSO study
  - For EDSS states 0-6 values from the TEMSO study were greater than the baseline values.
- Disutility of relapse from Orme et al., 2007
  - The disutility values are larger from Orme 2007 than Gani, which was used in the base case (relapse with hospitalisation −0.0589 vs. −0.0297; relapse without hospitalisation −0.0178 vs. −0.0089, respectively)
- Initial EDSS distribution from TOWER and TEMSO studies
  - The EDSS distribution in the trials covered a lower range than used in the base case (see page 237 of manufacturers submission)
- Starting age and female:male ratio from TOWER and TEMSO studies
  - The mean age was slightly lower in TOWER and TEMSO than the UK data (39.3 years vs. 37.9 years)
  - The female:male ratio was slightly lower in TOWER and TEMSO than the UK data (2.98:1 vs. 2.52:1)
- Natural history relapse rate from Patzold, 1982
  - These data analysed dates from 1976 to 1980, and estimated lower relapse rates
- Proportion of relapses leading to hospitalisation from placebo arms of TEMSO and TOWER studies
  - The base case uses data from Dee at al., which estimated a 20% hospitalisation rate and was considered to be more representative of the UK population. The rate in the TEMSO and TOWER studies was 30.7%.

- Probability of adverse events in subsequent years equal to adverse events in year 1
  - The base case assumes that some adverse event rates decrease after the first year, for example injection site reactions, hair thinning, and influenza like symptoms.

6.10 The manufacturer also presented fully incremental analyses that compared teriflunomide to the individual comparators. The manufacturer conducted scenario analyses using the base case (post 2000) MTC values, the 'All Years' MTC data, the 'All Years' MTC values without Bornstein et al, and the base case (post 2000) MTC values with the inclusion of treatment with licensed beta interferons in SPMS. In the probability analyses, teriflunomide dominated each of the individual comparators for the majority of scenarios with the following exceptions: 'All Years' MTC: £86,866 per QALY gained for teriflunomide compared with glatiramer acetate; 'All Years' MTC without Bornstein et al: £21,062 per QALY gained for teriflunomide compared with glatiramer acetate, and £301,857 per QALY gained for Rebif 22 µg compared with teriflunomide; and basecase MTC with SPMS treatment: and £105,604 per QALY gained for Rebif 44µg compared with teriflunomide.

6.11 The manufacturer presented cost effectiveness results for 2 subgroups; the HA and RES populations. These results are presented in Table 12. For the HA subgroup, teriflunomide dominated fingolimod. For the RES subgroup, teriflunomide was associated with an ICER of £63,107 per QALY gained compared with natalizumab.

Table 12 Manufacturer's cost effectiveness results for the highly active disease and rapidly resolving disease subgroups (Probabilistic Results)

Scenario		Treatment	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£)
Highly active disease	Fingolimod at £11,000 per year	Teriflunomide	[redacted]	[redacted]	-67,826	0.725	Teriflunomide dominates
		Fingolimod	[redacted]	[redacted]			
	Fingolimod	Teriflunomide	[redacted]	[redacted]	-35,084	0.746	Teriflunomide

	at list price	Fingolimod	[redacted]	[redacted]			dominates
Rapidly evolving disease		Teriflunomide	[redacted]	[redacted]	30,133	0.477	63,107
		Natalizumab	[redacted]	[redacted]			

In: Incremental; ICER: Incremental cost-effectiveness ratio; QALY: quality adjusted life year,

Evidence review group comments

6.12 The ERG reviewed the manufacturer's model and economic systematic review. The ERG commented that the manufacturer undertook a comprehensive, well rounded systematic literature review and provided a de novo cost effectiveness model that was flexible to sensitivity and scenarios analyses. During clarification, an error was identified in the manufacturer's model and was corrected throughout the ERG analyses shown below. Of note, teriflunomide dominates the comparator throughout much of the ERGs analyses when the PAS discount for teriflunomide is applied. Therefore the results without the PAS discount have also been presented to show the impact each scenario has on the ICER.

6.13 The ERG conducted some sensitivity analyses to determine the key areas of uncertainty in the manufacturer's model. The ERG's analyses compared teriflunomide with the blended comparator and also Rebif 44 µg, because it has head to head trial results. These analyses showed that the ICER increased compared to the blended comparator and Rebif 44 µg in all scenarios, with the exception of the scenario where an increased withdrawal rate was assumed. The ERG identified the following as the key drivers in the model and conducted scenario analyses to explore them further:

- The choice of comparator (see 6.14)
- The natural history and the rate of transition to SPMS (see 6.15)
- The hazard ratio of progression and the "waning" of the treatment effect (see 6.16)
- The health related quality of life associated with the more severe health states (see 6.17)

- The possible "double counting" of withdrawal when estimating the relative effectiveness of the treatments (see 6.18)

6.14 The ERG noted the use of a blended comparator in the base case of the manufacturer's model. The ERG commented that the choice of a blended comparator was inappropriate because they considered that it does not meet the NICE methods guide reference case, which requires 'best practice' to be used as the comparator. They stated further that the manufacturer's method for calculating the blended comparator, which used a weighted average of each individual treatments model inputs, is inappropriate, noting that 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, which reduced the ICER by a small amount (Table 13). 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 relative to placebo and sometimes in the opposite direction.

Table 13 Deterministic results using the ERG's calculation of the blended comparator (without PAS), compared to the manufacturer's corrected base case

Technology	Manufacturer's corrected base case (manufacturer's blended comparator)			ERG's calculation of the blended comparator		
	QALYs	Cost	ICER*	QALYs	Cost	ICER*
Blended comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*ICER of teriflunomide compared to selected technology

6.15 The ERG reviewed how disability progression was captured in the manufacturer's model. The ERG noted that the manufacturer had used the London Ontario dataset (published in 1989) for predicting the initial

distribution of EDSS and natural history progression of RRMS without DMT. The ERG stated that previous technology appraisals have questioned the applicability of the London Ontario data set because of changes in best supportive care and because it did not collect data on patients whose disease regressed to a better EDSS state. The ERG noted that a substantial proportion of patients in the TEMSO trial who experienced SAD later regressed. They also considered that the initial EDSS states and transition probabilities were taken from a population with more severe disease than the first-line population in which teriflunomide is expected to be used. The ERG therefore conducted an exploratory analysis using the initial EDSS distribution from the TEMSO and TOWER trials and found that it slightly reduced the ICER compared with the manufacturer's base case (Table 14). The ERG also used the TEMSO and TOWER data to estimate disability progression in two analyses, one for the patients with RRMS, and the other for patients with SPMS. Using the trial data to estimate the disability progression of patients with RRMS either slightly increased (compared with Rebif) or slightly decreased the ICERs (compared with the blended comparator) compared with the manufacturer's base case. The ERG also explored the effect of slowing the disease progression for patients in the SPMS by using the same trial-based transition probabilities for the RRMS states. This analysis showed that if patients with RRMS or SPMS progress through EDSS states at the same rate, the ICERs were markedly increased compared with the manufacturer's base case (Table 14). The ERG stated that this suggests that if disease progression for patients with SPMS is slower than that predicted by the London Ontario dataset then the manufacturer's base case ICERs may be underestimated. The ERG also estimated alternative conversion rates from RRMS to SPMS based on the London Ontario dataset, which resulted in a small increase in the ICERs (seeTable 15). With the PAS discount applied teriflunomide dominated Rebif and the blended comparator for each these disability progression scenarios.

Table 14 Comparison of the manufacturer's base case with the ERG's analysis of disability progression and EDSS distribution

		QALYs	Cost	ICER*	ICER with PAS
Manufacturer's corrected base case	Blended comparator	[redacted]	[redacted]	[redacted]	Not reported
	Rebif 44µg	[redacted]	[redacted]	[redacted]	Not reported
	Teriflunomide	[redacted]	[redacted]	[redacted]	
The results comparing differences in the initial distribution of EDSS *ERG: Initial EDSS distribution TEMSO + TOWER*	Blended comparator	[redacted]	[redacted]	[redacted]	Not reported
	Rebif 44µg	[redacted]	[redacted]	[redacted]	Not reported
	teriflunomide	[redacted]	[redacted]	[redacted]	
Results comparing disability progression in RRMS from London Ontario data (base case) to the placebo arms of the trials *ERG: TEMSO and Tower trial data for disability progression for RRMS*	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates
	Rebif 44µg	[redacted]	[redacted]	[redacted]	Teriflunomide dominates
	Teriflunomide	[redacted]	[redacted]		
Results comparing disability progression in SPMS from London Ontario data to the placebo arms of the trials *ERG: TEMSO and Tower trial data for disability progression for SPMS*	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates
	Rebif 44µg	[redacted]	[redacted]	[redacted]	Teriflunomide dominates
	Teriflunomide	[redacted]	[redacted]		
Results comparing conversion to SPMS as calculated by the manufacturer to those calculated by the ERG both using the London Ontario data *ERG: ERG corrected SPMS conversion using London Ontario natural history of progression*	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates
	Rebif 44µg	[redacted]	[redacted]	[redacted]	Teriflunomide dominates
	Teriflunomide	[redacted]	[redacted]	[redacted]	

*ICER of teriflunomide compared to selected technology, without PAS discount. Adapted from the ERG report Table 55, 58, 59, 61

6.16 The ERG noted that the effect of treatment on disability progression was estimated from the manufacturers base case MTC, stating that these data were not robust because of the exclusion of a large number of studies (by selecting only studies post-2000) and the heterogeneity across the studies that were included (see 4.22-4.25). They highlighted the following concerns:

- Betaferon was estimated to be less effective at slowing disability progression compared with best supportive care which raises issues about the validity of the MTC.
- The estimate of SAD for teriflunomide compared with Rebif 44µg from the MTC appeared to be more favourable towards teriflunomide compared with the direct head to head evidence in TENERE.
- Using the blended comparator means the effect size applied for beta-interferons favours teriflunomide compared with the estimates of 3 of the individual beta-inteferons included in the blended comparator.

The ERG conducted scenario analyses to explore the impact of different treatment effects. Firstly it used the TENERE trial data, rather than the MTC data to estimate the relative treatment effect for teriflunomide compared with Rebif 44 µg. Secondly, it tested the assumption that there was no difference in treatment effect between teriflunomide and Rebif 44 µg. Finally they used the 'All years' MTC data to estimate the relative treatment effect of teriflunomide. All 3 scenarios increased the ICER substantially. When the PAS price is applied, teriflunomide dominated the blended comparator or Rebif 44 µg in all scenarios.

Table 15 Comparison of the manufacturer's corrected base case with the ERG's amendments of the relative treatment effect of teriflunomide on progression

Analyses	Technology	QALY	Cost	ICER (without PAS)	ICER (PAS)
Manufacturer's corrected base case (teriflunomide HR = 0.71 vs. placebo)	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates both
	Rebif 44µg	[redacted]	[redacted]	[redacted]	
	Teriflunomide	[redacted]	[redacted]	[redacted]	
TENERE trial effectiveness (teriflunomide HR = 0.77 vs. placebo)	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates both
	Rebif 44µg	[redacted]	[redacted]	[redacted]	
	Teriflunomide	[redacted]	[redacted]	[redacted]	
Same effectiveness as Rebif 44µg	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates

(teriflunomide HR = 0.79 vs. placebo)	Rebif 44µg	[redacted]	[redacted]	[redacted]	both
	Teriflunomide	[redacted]	[redacted]	[redacted]	
'All Years' MTC (teriflunomide HR = 0.69 vs. placebo)	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates both
	Rebif 44µg	[redacted]	[redacted]	[redacted]	
	Teriflunomide	[redacted]	[redacted]	[redacted]	

6.17 The ERG commented on the utility values used in the model. It noted that the manufacturer's base case used values were derived from a 2005 UK MS Survey (Orme et al.) which has been criticised in previous NICE evaluations because of the low response rates, selection bias, unrepresentative population and self-reported severity. The ERG noted that the TEMSO trial had collected HRQoL data using the EQ-5D, although this only captured utility values for EDSS states 0-6. The ERG noted that the utility values from TEMSO [redacted] 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 it is more reflective of patients that are likely to receive teriflunomide as a first line treatment for RRMS. The ERG therefore conducted 4 scenarios using alternative utility values, as summarised in Table 16, which all resulted in higher ICER's for teriflunomide, however, when the PAS price is used, teriflunomide dominated the blended comparator and Rebif 44µg in all scenarios. The ERG considered that scenario 4 was the most representative of the patients being treated with teriflunomide because it used utility data from TEMSO (EDSS 0-6) for the baseline estimates of HRQoL and estimated utility differences between EDSS states 7-9 from a large UK-based survey (Orme et al.).

Table 16 Comparison of the manufacturers corrected base case with results of the ERG's HRQoL scenarios

Technology		QALY	Cost	ICER (without PAS)	ICER (with PAS)
Manufacturer's corrected base case	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates both
	Rebif 44 µg	[redacted]	[redacted]	[redacted]	
	Teriflunomide	[redacted]	[redacted]	[redacted]	
3. TEMSO + TA 127 *TEMSO data for EDSS states 0-6 and HRQoL data from TA 127 for EDSS states 7-9*	Blended comparator	[redacted]	n/a	[redacted]	Teriflunomide dominates both
	Rebif 44 µg	[redacted]	n/a	[redacted]	
	Teriflunomide	[redacted]	n/a		
2. TEMSO + averages *TEMSO data for EDSS 0-6 and an average of 4 studies for states 7-9*	Blended comparator	[redacted]	n/a	[redacted]	Teriflunomide dominates both
	Rebif 44 µg	[redacted]	n/a	[redacted]	
	Teriflunomide	[redacted]	n/a		
3. Averages *Average from 4 studies used for all EDSS states*	Blended comparator	[redacted]	n/a	[redacted]	Teriflunomide dominates both
	Rebif 44 µg	[redacted]	n/a	[redacted]	
	Teriflunomide	[redacted]	n/a		
4. TEMSO + Orme differences *TEMSO data for EDSS 0-6 and the differences between states 7-9 observed in the Orme et al 2007 study was used to calculate states 7-9 from the TEMSO data.*	Blended comparator	[redacted]	n/a	[redacted]	Teriflunomide dominates both
	Rebif 44 µg	[redacted]	n/a	[redacted]	
	Teriflunomide	[redacted]	n/a		

*ICER of teriflunomide compared to selected technology

6.18 The ERG considered the discontinuation rates applied in the model. The ERG noted that the manufacturer assumes that discontinuation decreases after 2 years because patients will have adjusted to treatment use and those who do not tolerate treatment will have discontinued. The ERG stated that this assumption is not supported by any evidence and the manufacturer did not consider the alternative possibility that discontinuation increases because of a loss of response or poor compliance which may influence longer term discontinuation and may not be captured by the short duration of the teriflunomide trials. The ERG

commented that withdrawal can have an important and perverse effect on the ICER. The ERG stated that increasing withdrawal can result in patients being treated with best supportive care more quickly, which is associated with lower costs than the comparators (beta-interferon and glatiramer acetate), which themselves are not cost-effective. The ERG state therefore that an increased withdrawal rate can reduce the ICER.

6.19 The ERG reviewed the costs included within the manufacturer's model. They noted that the manufacturer had stated that costs used in the model were conducted from an NHS and PSS perspective and, that only resources relevant to the management of MS were considered. The ERG commented that there is uncertainty surrounding which costs were included in some of the sources used, particularly the direct non-medical costs for the EDSS states. Furthermore, it noted that 1 source of costs (Karampampa et al, used in sensitivity analyses) included informal care costs such as productivity losses of the working caregivers, and these do not meet the perspective specified in the NICE reference case. The ERG investigated the impact of excluding non-health costs, which increased the ICERs. However, when the PAS discount was applied, teriflunomide dominated the blended comparator and Rebif 44 µg.

Table 17 Comparison of the manufacturer's base case which included non-health costs with the ERG's analysis omitting without non-health costs

Analysis	Technology	QALYs	Cost	ICER without PAS	ICER with PAS
Manufacturers corrected base case (Including non-health costs)	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates both
	Rebif 44 µg	[redacted]	[redacted]	[redacted]	
	Teriflunomide	[redacted]	[redacted]	[redacted]	
ERG's analyses (excluding non-health costs)	Blended comparator	[redacted]	[redacted]	[redacted]	Teriflunomide dominates both
	Rebif 44 µg	[redacted]	[redacted]	[redacted]	
	Teriflunomide	[redacted]	[redacted]	[redacted]	

*ICER of teriflunomide compared to selected technology

6.20 The ERG presented an exploratory analysis that comprised of their preferred parameters as follows:

- Trial distribution of initial EDSS
- Trial estimates of natural history
- ERG calculation of SPMS conversion
- Treatment effects from the 'All Years' MTC
- Trial based HRQoL and changes from Orme et al.
- Exclusion of non-health costs

The resulting ICERS (with the teriflunomide PAS) were similar to those in the manufacturer's base case, although the total QALYs were much higher and the total costs much lower for each intervention (Table 18). The ERG noted that the increase in total QALYs is because of the assumptions that the patient's disease is less severe when they start treatment, that the model allows for improvements in disability (EDSS), and because utility values are more closely related to the trial values. The decrease in total costs was largely explained by the exclusion of non-health costs. The results of the ERG's probabilistic analysis show that teriflunomide is more effective and more costly than glatiramer acetate resulting in an ICER of £107,148 per QALY gained. However, teriflunomide dominates Rebif 44 µg and the blended comparator. Because of the uncertainty associated with the manufacturer's MTC, the ERG also presented their preferred analysis using the manufacturer's base case MTC (post 2000), rather than the 'All Years' MTC. The ERG's deterministic analysis resulted in an ICER of £6,226 per QALY gained for teriflunomide compared with glatiramer acetate while all other comparators were dominated.

Table 18 Comparison of manufacturer's base case with the ERG's preferred scenario's (with PAS)

Technology	Manufacturer's corrected base case with PAS price	ERG's preferred analysis with PAS price

	QALYs	Cost	ICER	QALYs	Cost*	ICER**
Probabilistic results - full incremental analysis ('All Years' MTC)						
Glatiramer acetate	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Rebif 22µg	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	£917,667
Rebif 44µg	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated
Avonex	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated
Betaferon	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated
Teriflunomide	[redacted]	[redacted]	Dominates	[redacted]	[redacted]	£107,148
Probabilistic results - Selected comparators ('All Years' MTC)						
Blended comparator	[redacted]	[redacted]	Teriflunomide Dominates	[redacted]	[redacted]	Teriflunomide Dominates
Rebif 44µg	[redacted]	[redacted]	Teriflunomide Dominates	[redacted]	[redacted]	Teriflunomide Dominates
Teriflunomide	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Deterministic results - full incremental analysis with base case MTC (post 2000 MTC).						
Glatiramer acetate	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Rebif 22µg	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated
Rebif 44µg	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated
Avonex	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated
Betaferon	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated
Teriflunomide	[redacted]	[redacted]	£86,946	[redacted]	[redacted]	£6,266

* Not ordered by cost for easier comparison to the base case results. ** Comparisons top teriflunomide, except teriflunomide which is compared to glatiramer acetate *** The same by chance

6.21 The ERG did not consider the subgroup analyses to be reliable because of the very small number of patients included in each of the teriflunomide groups, and because the relative risks and hazard ratios were calculated from the specified subgroups combined with the natural history of the of the full RRMS population. 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 the RES and HA populations), the manufacturer did not provide subgroup analyses which excluded the RES and HA populations. Furthermore, it stated that only results from the TEMSO trial were used to calculate the teriflunomide effects. The ERG used the manufacturer's corrected model, and assumed that patients on teriflunomide have the same effectiveness as the full RRMS population, to

calculate the ICERs for teriflunomide in the RES and HA populations (i.e. compared with natalizumab and fingolimod respectively, which were [redacted] per QALY gained, respectively. The PAS price for fingolimod was not applied.

7 Equality issues

7.1 No equality issues have been raised through the scoping process, or in any of the submissions.

8 Innovation

8.1 The manufacturer stated in their submission that teriflunomide should be considered innovative because it is an oral therapy.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

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

Under development

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

- Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication January 2014.
- Alemtuzumab for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication April 2014.
- Laquinimod for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication October 2014.