NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Teriflunomide for treating relapsing–remitting multiple sclerosis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Genzyme	**Section A: Has all of the relevant evidence been taken into account?** Genzyme do not believe all relevant evidence has been considered as relates to the following three areas (A1. to A.3.) **A.1. Relevant evidence showing the comparison of the output from the post 2000 and all years MTCs as it relates to direct trial evidence for glatiramer acetate versus placebo has not been considered in the ACD.** The output of the post 2000 MTC and all years MTC has been compared within the ACD to determine which of the two MTCs provides the closest match to direct trial data. This is described on page 25 of the ACD in relation to teriflunomide versus Rebif 44µg MTC results compared to the direct evidence from the TENERE study and direct evidence of betaferon versus placebo. This has been done to provide supporting evidence as to which of these two MTCs should be considered to provide the most precise estimate of the efficacy of teriflunomide relative to its comparators (the beta interferons and glatiramer acetate). This consideration resulted in the statement on page 21 of the ACD "It (ERG) also noted that the results of the 'all years' MTC were more consistent with the direct trial results". The choice of MTC used to provide efficacy estimates for the cost effectiveness model is identified as of key importance. We would therefore highlight the importance of MTC choice regarding its impact on the incremental cost-effectiveness ratio of teriflunomide compared to glatiramer acetate. Teriflunomide is cost effective against all comparators using the all years MTC and the post 2000 MTC with the exception of glatiramer acetate against which it is cost effective using the post 2000 MTC results but not when using the all years MTC results. A comparison to the results of the four trials that provide direct evidence of the efficacy of glatiramer acetate versus placebo to the output of the two MTCs is useful and we would argue the most pertinent direct evidence to consider in this circumstance. The output of the MTCs as they relate to ARR, discontinuation rates and SAD 3 HR are shown below in Table A.1. for glatiramer acetate versus placebo.	Comments noted. The Committee agreed that the most appropriate MTC was the 'all years' MTC adjusted for baseline relapse rates (see FAD section 4.7) .

Consultee	Comment	Response
Genzyme		Comments noted. The Committee agreed that the most appropriate MTC was the 'all years' MTC adjusted for baseline relapse rates (see FAD section 4.7) .

Table A.1: Comparison of the MTC outputs to direct trial evidence for glatiramer acetate and teriflunomide

Comparison	Post-2000, MTC	All Years MTC (unadjusted)	Direct Evidence	Trial Name and sample size	Author, Year
Annualized relapse rate, rate ratio (95%CrI)					
GA vs. placebo	0.64 [0.53, 0.76]	[redacted]	0.72 [0.61, 0.87] 0.7 [0.57, 0.86] 0.67 [0.48, 0.93]	CONFIRM (n=713) Copolymer 1 MS Study (n=151) European/Canadian GA Study (n=139)	Fox, 2012 Johnson, 1995 Comi, 2001
Teriflunomide 14 vs. placebo	0.67 [0.57, 0.77]	[redacted]	0.68 [0.36, 1.27] 0.69 [0.58, 0.81] 0.64 [0.53, 0.77]	O'Connor, 2006 (n=118) TEMSO (n=722) TOWER (n=761)	O'Connor, 2006 O'Connor, 2011 Kappos, 2012
Three-months sustained accumulation of disability, hazard ratio (95%CrI)					
GA vs. placebo	0.93 [0.59, 1.45]	[redacted]	0.93 [0.63, 1.37] 0.32 [0.09, 1.09] 0.86 [0.51, 1.45]	CONFIRM (n=713) Bornstein, 1987 (n=50) Copolymer 1 MS Study (n=151)	Fox, 2012 Bornstein, 1987 Johnson, 1995
Teriflunomide 14 vs. placebo	0.71 [0.53, 0.92]	[redacted]	0.7 [0.51, 0.96] 0.68 [0.47, 1]	TEMSO (n=722) TOWER (n=761)	O'Connor, 2011 Kappos, 2012
Discontinuation rate, odds ratio (95%CrI)					
GA vs. placebo	[redacted]	[redacted]	0.59 [0.43, 0.81] 1.15 [0.57, 2.33] 1.01 [0.34, 2.97]	CONFIRM (n=713) Copolymer 1 MS Study (n=151) European/Canadian GA Study (n=139)	Fox, 2012 Johnson, 1995 Comi, 2001
Teriflunomide 14 vs. placebo	[redacted]	[redacted]	3.8 [1.15, 12.58] 0.9 [0.65, 1.25] 1.07 [0.79, 1.45]	O'Connor 2006 (n=118) TEMSO (n=722) TOWER (n=761)	O'Connor, 2006 O'Connor, 2011 Kappos, 2012

The following observations are thought to be of relevance in relation to Table A.1:

- Four randomized clinical trials (RCTs) were identified from the systematic literature reviews that provide direct evidence for glatiramer acetate versus placebo. Two RCTs, Fox 2012 and Johnson 1995, report annualized relapse rate, three months sustained accumulation of disability, hazard ratio (SAD-HR) and discontinuation rate (DR). Comi 2001 reports ARR-RR and DR, when Bornstein 1897 reports sufficient disability data to infer 3 months SAD-HR.
- The 3 month SAD HR data should be the primary focus of attention because the cost effectiveness results are substantially driven by this parameter value. For the two larger trials of glatiramer versus placebo, Fox 2012 (0.93) and Johnson 1995 (0.86) the estimates of the SAD HR 3 months from the clinical trials are closest to post 2000 MTC output (0.93) than the unadjusted all years MTC ([redacted]). The output from the small Bornstein 1987 study (0.32) is substantially different from the output from both MTCs. The results of the Bornstein study are in fact an outlier in relation to all beta interferon studies vs placebo (0.62-0.93) (IFNB ms Study Group 1993, PRISMS 1998) as well as the other two glatiramer acetate studies. Teriflunomide versus placebo SAD HR direct evidence data is similar to the output from both the post 2000 years MTC and the unadjusted all years MTC.

Consultee	Comment	Response
Genzyme	• The HE model is to some extent sensitive to discontinuation rate (DR) although to a substantially less degree than to SAD HR. For glatiramer, both MTCs provide similar DR output suggesting glatiramer has a lower discontinuation rate than placebo ([redacted]). The largest study CONFIRM (n=713) supports a lower than placebo discontinuation rate (0.59) closest to the output from the post 2000 MTC whilst the other two studies had higher than placebo discontinuation rates (1.01 and 1.15). For teriflunomide output from both MTCs provide similar output suggesting discontinuation rates close to placebo ([redacted]); the TEMSO study suggest slightly lower than placebo discontinuation rates (0.9) and TOWER slightly higher (1.07) with the smaller O'Connor et al study demonstrating substantially higher discontinuation rates than both. Discontinuation rates are likely to be impacted substantially by trial protocols which have the potential to cause a substantial deviation between discontinuation seen within trials compared to those seen in clinical practice. • The model is not sensitive to ARR RR results and these do not vary substantially across the two MTCs for glatiramer or teriflunomide versus placebo	Comments noted. The Committee agreed that the most appropriate MTC was the 'all years' MTC adjusted for baseline relapse rates (see FAD section 4.7) .
	A.2. Relevant evidence has not been considered relating to the decision in the ERG's preferred cost effectiveness analysis of using the TEMSO TOWER placebo arm to derive natural history disease progression data in the model. This evidence describes the high regression rates in higher EDSS states obtained using the TEMSO TOWER data and how this does not match clinical experience nor the output from another large natural history dataset. The following important points need to be noted: • Over the study period, the sample size of the data used to estimate transition probabilities in EDSS states 6 or above was too small to derive accurate transition probabilities (provide number of transitions from 6). This in accordance with: O The inclusion criteria for TEMSO and TOWER studies related to EDSS score were 0 to 5. O Duration of the studies: two years for TEMSO and for TOWER a median study treatment duration of about 1.5 years. O There were 743 placebo patients included within the TEMSO-TOWER matrix In addition the short time period of the period over which transitions were observed using the TEMSO-TOWER placebo arm data (2 years) makes it inappropriate to use for a life time health economic model. The London Ontario with follow up data (mean: [redacted] years) over a longer time period seems more appropriate for use in a life time model	Comments noted. The Committee understood the impact on the ICER, and the limitations of using the placebo arms of the TEMSO and TOWER trials to estimate the natural history of disease progression but agreed that using the data from the placebo arms of the TOWER and TEMSO trials was appropriate for modelling disease progression (See FAD section 4.15).

Consultee	Comment	Response
Genzyme	The transition probabilities in these higher EDSS states (6 and above) derived using the TEMSO-TOWER matrix suggests a high level of regression when evidence from clinical practice suggests that patients who have reached an EDSS state of 6 (walking with support) or higher experience much more infrequent improvement. Whilst on page 38 of the ACD it is stated that "It (the Committee) agreed that it was appropriate to allow modeled patients to move to lower as well as to higher EDSS states … which is line with what is seen for lower EDSS states" no consideration is given to the fact that this is not appropriate for patients in higher EDSS states and what the implication of assuming high regression rates in these patients has upon the output from the HE model and ICER estimates. The model is sensitive to the assumptions made about regression in these higher EDSS states shown by the fact that using a transition matrix made of TOWER and TEMSO placebo arms from EDSS 0 to 5 but using London Ontario to source EDSS 6 to 8 (where no regression is assumed) leads to the probabilistic upper range ICER result of teriflunomide versus glatiramer acetate reducing from £107,000 (as stated in the ACD on page 42) to £81,000. Comparing TEMSO TOWER placebo matrix data to one recent analysis of untreated MS patients in the British Columbia MS database over the period 1980 to 2009 (Tremlett et al. Natural, innate improvements in multiple sclerosis disability. Mult Scler 2012 18: 1412-1421] leads to the following relevant points: •88% of the British Columbia patients had relapsing onset MS (only 12% had primary progressive MS) •Amongst the 2472 MS suffers in the British Columbia dataset with EDSS 6 and above annual improvement occurred in 10.6% which is much lower than the regression rates for untreated patients after one year obtained using data from the TEMSO-TOWER placebo matrix in the HE model ([redacted]%, [redacted]% and [redacted]% for EDSS 6, 7 and 8 patients respectively). •It would be more appropriate, if the TEMSO-TOWER placebo matrix is to be used for these higher EDSS states, to use data from the London Ontario data set (mean follow up: 22 years) which would assume no regression amongst these patients. •It should also be noted that the rates of regression observed in the Canadian study were substantially lower for EDSS states below 6 compared to those obtained after one year using the TEMSO-TOWER placebo matrix within the HE model (15.3% for the 3135 MS suffers with EDSS 1-3 compared to [redacted]%, [redacted]% and [redacted]% for EDSS 1, 2 and 3 respectively using the TEMSO-TOWER matrix and 20.4% for the 1668 MS sufferers with EDSS 4-5.5 compared to [redacted]% and [redacted]% for EDSS 4 and 5 respectively using the TEMSO-TOWER matrix). This would call into question the validity of using the high regression rates derived using the TEMSO-TOWER matrix within the model. • The invalidity of these high regression rates is further supported by the fact that the untreated patients reported annually as staying in the same EDSS state was 53% in the analysis of the British Columbia data set which is higher than the [redacted]% of untreated patients dependent on EDSS state who stay the same after one year if the TEMSO-TOWER placebo matrix is used in the HE model.	Comments noted. The Committee understood the impact on the ICER, and the limitations of using the placebo arms of the TEMSO and TOWER trials to estimate the natural history of disease progression, but agreed that using the data from the placebo arms of the TOWER and TEMSO trials was appropriate for modelling disease progression (See FAD section 4.15).

Consultee	Comment	Response
Genzyme	• Patients in the British Columbia dataset reported as getting worse annually by at least one EDSS point or more was 20.5% with an additional 32.9% getting worse by 0.5 EDSS points which is not inconsistent with the [redacted]% of untreated patients dependent on EDSS state who get worse by at least one EDSS state after one year in the HE model if the TEMSO-TOWER placebo matrix is used (the model does not capture EDSS changes of less than one point) and is not inconsistent with the [redacted]%-[redacted]% who get worse by at least one EDSS state after one year in the HE model if the London Ontario matrix is used. **A.3. Relevant evidence to support the inclusion of direct non-medical costs sourced from Tyas et al 2007 within the cost effectiveness analysis which were excluded in the ERG's preferred analysis.** The ERG considered there to be insufficient evidence to support the inclusion of direct non-medical costs sourced from Tyas et al 2007 in the cost effectiveness model because of a lack of detail within the Tyas et al publication as to what is included within these costs and hence it cannot be clarified whether their inclusion meets the requirements of the NICE reference case. This led to the exclusion of non-health costs in the ERG's preferred analysis as outlined on page 27 of the ACD. However, the following evidence supports the inclusion of these costs: • Although no details of what was meant by direct non-medical costs exist in the Tyas paper the direct non-medical costs within this paper equate to those found in the Karampampa et al 2012 [1] paper which are also UK specific costs (see Table A.3.1. below) where details of what is included in this category are provided. The table shows costs from Karampampa limited to professional non-medical support with and without the inclusion of investments / modifications. Investments / modifications were defined in a separate paper (Karampampa et al 2012 [2]) as home modifications, car modifications, walking stick, wheelchairs. Professional non-medical support is split between home help (mean 37 hours a year) and professional help unspecified (mean 20 hours a year) • The UK MS Survey carried out by the MS Society suggests that 50% of MS patients have their social care paid for entirely by the government and another 33% have their social care partly paid for by the government. Table A.3.1 also shows the direct non-medical costs from Karampampa reduced by 33% to take into account that 17% of patients will pay for social care entirely from their own pocket and 33% partially from their own pocket (MS Society report 2013). These costs are still comparable to those in Tyas et al. • The substantial increase in direct non-medical costs in higher EDSS states is supported by the results of the UK MS Survey which showed that 10% of patients requiring occasional assistance and 60% of those requiring constant assistance received social care (MS Society report 2013). A report from the Work Foundation also identified high costs associated with the higher dependency states of MS; high dependency home care of £1,345 per week, stay at a residential home of £758 a week and maintenance of a special needs flat of £933 per week (Work Foundation report 2011)	Comments noted. The Committee understood the impact on the ICER of including or excluding non-health costs. The Committee agreed. The Committee concluded 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 (see FAD section 4.19).

Consultee	Comment	Response
Genzyme	**Table A.3.1: Comparing UK direct non-medical costs in Tyas et al to non-medical professional support and investments / modifications costs in Karampampa et al.**	

EDSS state	Tyas et (included in manufacturer basecase submission)	Karampampa et al (uplifted to 2013/14)	Karampampa et al - 66% (uplifted to 2013/14)
0	£5,335	£0-£53	£0-£35
1	£5,780	£0-£53	£0-£35
2	£6,735	£0-£53	£0-£35
3	£9,565	£0-£53	£0-£35
4	£6,462	£1055-£2671	£703-£1780
5	£9,489	£1055-£2671	£703-£1780
6	£9,811	£1055-£2671	£703-£1780
7	£15,761	£18241-£21558	£12160-£14371
8	£20,811	£18241-£21558	£12160-£14371
9	£12,915	£18241-£21558	£12160-£14371

Section B: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Genzyme do not believe that the ACD provides summaries of the clinical and cost effectiveness which are reasonable interpretations of the evidence in relation to the two areas below

B.1. The interpretation of the cost effectiveness evidence in the ACD is not reasonable because it gives no positive weighting for the fact that teriflunomide has been assessed as being cost effective versus the beta interferons.

The following points are noted:

• Teriflunomide will be used in place of beta interferons in an estimated 76% of cases (and glatiramer acetate in 24% of cases). The appraisal does not identify uncertainty or concern about the cost effectiveness of teriflunomide versus the beta interferons only versus glatiramer acetate

In the NICE appraisal of fingolimod, a blended comparator was used by NICE to determine the cost effectiveness of fingolimod. A consideration therefore was made of the cost effectiveness of fingolimod in relation to each of the beta interferons and glatiramer acetate. Three points are noted in relation this:

o The ACD has rejected the use of a blended comparator for the assessment of teriflunomide which is inconsistent given that one was requested and accepted for use by the Appraisal Committee for the NICE appraisal of fingolimod.

o It is noted that on page 21 section 3.27 of the ACD it is stated “It (the ERG) regarded this (the use of a blended comparator) as inappropriate because it noted that it does not meet the NICE methods guide reference case, which needs ‘best practice’ to be used as the comparator.” The NICE methods guidance states on page 23 Section 2.2.4. “Relevant comparators are identified, with consideration given specifically to

Comments noted. The FAD states that teriflunomide dominates the beta-interferons (see section 4.22).

The Committee agreed that the manufacturer’s revised base case reflected the Committee’s preferred analyses, that is, the results were presented incrementally for all comparators (see section 4.11). A fully incremental analysis is the preferred approach. Occasionally the Committee has considered it necessary to also consider blending of comparators appropriate. In this appraisal blending of comparators was not required for decision making.

Consultee	Comment	Response
Genzyme	routine and best practice in the NHS (including existing NICE guidance)…" [Guide to the methods of technology appraisals June 2008 as applies to this appraisal]. It is wrong to assert that NICE methods guidance refers solely to best practice to be used as the comparator since it also refers to routine practice. The blended comparator since it captures use weighted by percentage usage amongst comparators can be said to be reflecting routine use. o Given that the use of a blended comparator has been rejected, no apparent weighting has been given in the ACD to the fact that teriflunomide is considered cost effective against the beta interferons for which it will substitute in 76% of cases. **B.2. The ACD wrongly summarises the evidence provided by the manufacturer in relation to the cost effectiveness of teriflunomide as relating exclusively to first line use of the drug.** It is wrong to consider data presented by Genzymein its' submission to relate exclusively to first line use of the drug.. This was a comment made by Genzyme as an error made in the ERG report. It is the belief of the manufacturer that this error has led to the use of teriflunomide within the ACD being mentioned exclusively in relation to first line use (for example on pages 45 and 47 of the ACD). It is appropriate to consider data presented by Genzyme as it relates to teriflunomide use in place of beta interferons and glatiramer acetate which includes but is not limited to first line use. We note the following in relation to Genzyme's submission to NICE to support this view: • Within the HE section, the manufacturer has presented a cost effectiveness analysis that relates to both treatment naïve and treatment experienced patients. It is an incorrect assumption within the ERG report reflected in the ACD that the manufacturer has submitted a cost effectiveness analysis that relates exclusively to treatment naïve patients. • Within the manufacturer's submission the anticipated use of teriflunomide is stated to be in place of glatiramer and beta interferons. No mention is made of this being exclusively in first line use. For example: O Page 18 "we anticipate that teriflunomide will be used in patients with RRMS who otherwise would receive beta-interferons or glatiramer acetate." O Page 25: "The positioning of teriflunomide is as an alternative to beta-interferons or glatiramer acetate" O Page 42: "It is anticipated that teriflunomide will be used in RRMS where beta-interferons or glatiramer are currently prescribed. Teriflunomide provides an alternative option." O Page 215 "We expect teriflunomide to be used in clinical practice in both pre-treated and treatment-naive patients; therefore the mixture of these two populations within the trials is representative. We perceive teriflunomide's place in the treatment pathway to be similar to the interferons and glatiramer, and as such would be prescribed prior to, as an alternative to, or after either of these therapies. Interviews with KOLs about this positioning have revealed that patients routinely swap between the interferon brands and glatiramer; teriflunomide adds to these options [Genzyme KOL interview report, 2013]". O Page 224: "There was not a clear typical treatment pathway; the interviewed clinicians had patients which were being treated with a range of beta-interferons and glatiramer acetate at first and second line." O Pages 331-340 in Section C "Implementation" in which the place in therapy of teriflunomide is described in relation to estimating budget impact no mention is made of limiting to the use of the drug to treatment naïve	Comment noted. This was not the intention of the ACD. The Committee considered teriflunomide as an alternative to beta-interferons and glatiramer acetate. The Committee concluded that teriflunomide could be considered an effective use of NHS resources for treating adults with relapsing–remitting multiple sclerosis for whom beta interferons and glatiramer acetate would otherwise be considered as treatment options, section 4.23 of FAD.

Consultee	Comment	Response
Genzyme	patients because the drug is not expected to be used exclusively in treatment naïve / first line patients. **Section C: Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Given that Genzyme do not believe that all of relevant evidence has been taken into account and that the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence as outlined above we do not believe that the provisional recommendations are sound and a suitable basis for guidance to the NHS	Comment noted. No changes required.
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below: **i) Has the relevant evidence been taken into account?** The evidence considered seems reasonable and comprehensive. We have nothing to add here except to comment on the lack of neurology experts on the appraisal committee. We, however note that the committee sought personal perspective from clinical experts and patient.	Comment noted. The area of speciality of physicians is not a prerequisite to standing as a Committee member. We ask for nominations of clinical specialists and patient experts and the chair will consider these applications with a view on who will be best placed to advise the committee. Please see the terms of reference for further information on the Appraisal Committee.
	ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The document appears not to be focussing on cost effective solutions for a long term condition. It is a very technically dominated analysis of an economic model. There is a danger that this means the consultation and outcome are being swamped by hypothetical manipulation of mathematical data.	Comments noted. The decision at the first Committee meeting was a 'minded no' that sought further economic data from the manufacturer. All clinical data and health benefits were discussed fully see sections 4.5, 4.7, 4.8, 4.9, 4.10 and 4.21 of the FAD.

Consultee	Comment	Response
Royal College of Nursing	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The provision of a first line oral disease modifying drugs is innovative, this is recognised by the Committee within the report but it is overwhelmed by the mathematical modelling. An oral therapy may well lead to better adherence and much improved outcomes. There is an assumption by the Committee that there is a universal treatment pathway in place, this is not the case and therefore, we consider that the Committee cannot make assumptions on sequence or escalation of treatments.	Comment noted. 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. See section 4.21 of FAD.
	Treatment sequencing suggested is not a route that would generally be followed within practice; therefore it is not clear why it need further comparison in this way? People with multiple sclerosis who are offered disease modifying drugs need to be offered a range of options in order to make informed choices with their future care and treatment. Teriflunomide will sit within the costs of injectable disease modifying drugs and would therefore, offer far greater scope and choice for patients rather than only an injectable drug. We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with multiple sclerosis. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. 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. However, the Committee concluded that the analysis of individual drugs (without a sequence) was basis for decision-making in this appraisal See FAD section 4.20.
	Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted. No changes required.

Consultee	Comment	Response
United Kingdom Clinical Pharmacy Association	**1. Has all the relevant evidence been taken into account?** Answer: Yes, all relevant evidence has been taken into account. The limitations of the available trials and related analysis have been identified and additional information has been requested where appropriate. We agree with the concerns that the total number of available trials is small; the duration of the trials is not particularly long in relation to the likelihood of occurrence of relapses and the trials may have been too heterogenic for data pooling. Consideration was given to evidence related to clinical effectiveness, quality of life and economical aspects as well as clinical experts and affected patients. **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Answer: Yes. The evaluation of clinical effectiveness focuses mainly on the EDSS score which does not capture other symptoms such as fatigue, bladder symptoms, cognitive impairment and depression. There appears to be a considerable high amount of undisclosed evidence which was not accessible for interpretation. We agree with the criticism of the ERG that trial data before 2000 was excluded in the base-case analysis. We are also in agreement with the concerns regarding the use of a blended comparator. The proposed arguments for these concerns appear correct and reasonable. However, in absence of any other oral first line treatment, we would like to emphasise that an oral medication is a desirable option for patients who experience adverse effects from the injectables. We noted the lack of evidence for teriflunomide in rapidly evolving severe relapsing-remitting MS and highly active MS; although the suggested treatment pathway describes use of Natalizumab and Fingolimod for these patient groups, teriflunomide may still need to be considered as an option (treatment failure, side effects) before supportive care. **3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Answer: Yes, the reason for the provisional recommendations is clear and in view of the calculated ICER range understandable. **4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Answer: No	Comments noted. Teriflunomide is recommended as an option for treating RRMS. See section 1 of the FAD. 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 see section 4.21 of FAD.

Consultee	Comment	Response
MS Society	The MS Society welcomes the opportunity to respond to the ACD for teriflunomide in treating relapsing remitting multiple sclerosis. We include the views of people with MS as well as those of a number of expert medical advisors specialising in MS. We are very disappointed that the Committee's draft recommendation reports that there is insufficient evidence to support teriflunomide as a cost effective medicine to be made available in the NHS. We urge NICE to reconsider its decision on teriflunomide for the treatment of relapsing remitting multiple sclerosis for the following reasons: 1.Potential to significantly enhance quality of life, which, as accepted by the Committee, was not fully captured in the QALY 2.Clinical effectiveness in reducing relapse rates compared to a placebo, as recognised by the Committee in the ACD 3.Innovative benefit of teriflunomide in offering a first-line oral (and therefore convenient) treatment option with a favourable adverse effects profile 4.Wider benefits of teriflunomide including enabling a person to live with less requirement for care and support and the potential to remain in work 5.Cost effectiveness based on the relative pricing of other first-line treatments Further details on our reasons are provided here and we also refer NICE to our previous submission on the single technology appraisal of teriflunomide. **1. Evidence from people with MS** The Committee highlighted that, as an oral treatment, teriflunomide offered a step change for treating people with relapsing remitting multiple sclerosis which could have a substantial impact on quality of life. The MS Society strongly agrees with this opinion; and shares the Committee's view that the quality of life benefits of an oral treatment were not fully captured in the QALY. For this reason we ask the appraisal committee to take into full consideration and appropriately weight the views and experiences of people with MS. People with MS fear the residual disability a relapse may cause, which can vary from mild to severe, and which is unpredictable in nature. In our survey of more than 1000 people with relapsing remitting MS, 78 per cent said that they always or often worry about how their relapse impacts on those around them; 95 per cent were unable to maintain activities during a relapse and 90 per cent considered that relapses result in a lack of independence. The patient representative giving oral evidence to the Committee stressed that once on teriflunomide, she was able to stay employed and take part in family life. NICE must give due weight to the physical and emotional impact of relapses and not underestimate the potential for this treatment to significantly enhance quality of life.	Comments noted. The decision at the first meeting was a 'minded no' that required the manufacturer to present some further economic analysis. The Committee concluded in the FAD that teriflunomide should be recommended as an option for RRMS see section 1 of the FAD. 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. See section 4.21 of FAD.

Consultee	Comment	Response
MS Society	**2. The proven efficacy of teriflunomide** The MS Society agrees with the conclusion of the Committee that 'teriflunomide was clinically effective in reducing relapse rates compared with placebo, and that it may have a beneficial impact on accumulation of disability' (4.4, page 34). The worrying, painful and distressing nature of a relapse and the loss of independence, are all a fundamental concern for people with MS, having a great impact on quality of life. The evidence shows that patients being treated with teriflunomide experienced 30 per cent reduction in the number of relapses, which is similar to current first-line therapies. There is a clear professional consensus that treating people early with the most effective treatment is essential to preserve people's quality of life. Removing the option of any one effective treatment would be to condemn some people unnecessarily to a life governed by debilitating relapses and the accumulation of disability. The MS Society is concerned that an assumption of waning of treatment effect has been included in the ACD, without any evidence being provided to substantiate such an assumption or the reduced efficacy that the Committee perceives. We would like to know the evidence behind this conclusion, particularly in respect of the assumption that there will be a 50% decrease in treatment effect after 5 years. **3. The value of innovation** The Committee deemed teriflunomide to be an innovative technology, a view with which the MS Society would wholly agree, given the markedly different method of administration compared to current first-line injectable MS therapies. As the Kennedy report recommended, innovation should be considered and appropriately weighted as part of the decision making process. Teriflunomide meets many of the health-related benefits criteria listed by Kennedy including: • the ability to offer a different mode of administering a drug – in this case, a tablet rather than an injection or infusion for first-line treatment; • the opportunity to be treated at home rather than attend a hospital or clinic; • improvement in quality of life including enjoyment of greater dignity and independence – this treatment will give people with MS and their carers greater freedom; • the ability to minimise the social visibility of disease or care – a tablet can be taken more discretely and is less disruptive than infusions or injections. It is not clear from the ACD to what extent the above factors have formally been taken into account by the committee, or how each may have been weighted in the decision making process. Over 95% of 1000 people with MS said that a pill would be their treatment method of choice . The patient satisfaction data referred to in the ACD also shows a greater preference for teriflunomide when compared to Rebif-44: 'At week 48 the global satisfaction score was statistically significantly higher with teriflunomide than Rebif-44 (higher score indicates better satisfaction; 68.818 compared with 60.975, p=0.0162)' (3.5, page 9).	Comments noted. 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. See FAD section 4.18. Comments noted. 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. See section 4.21 of FAD. The Committee concluded that teriflunomide could be considered an effective use of NHS resources for treating adults with relapsing–remitting multiple sclerosis for whom beta interferons and glatiramer acetate would otherwise be considered as treatment options, section 4.23 of FAD.

Consultee	Comment	Response
MS Society	NICE should note that the clear preference for a pill as a preferred treatment method is based on the following factors: • added convenience and therefore enhanced quality of life • physical and psychological barriers to injecting • freedom from injection site reactions • ease of administration and less dependence on a friend, family member or carer The Committee heard from the patient representative who gave evidence that using injectable treatments had been a 'dark part' of her life, including being ill for 2 days after the injection and worrying for the following 5 days about the next injection. Enhancing quality of life for people with MS and their carers should be a fundamental concern for NICE. We therefore strongly encourage NICE to consider the evidence provided by people with MS regarding their preference for an oral treatment option, particularly as teriflunomide would provide the first oral option as a first-line therapy. Additionally, the inconvenience of a treatment is compounded by the additional healthcare costs due to extra appointments required to help manage side effects and help with problems related to injections. **4. Wider benefits of treatment** The ACD accepts that quality of life benefits of an oral treatment were not fully captured in the QALY, but there are additional wider benefits to which we feel that NICE should give more consideration. As the Kennedy report stated, the wider benefits that should be taken into account include: • ability to join the workforce • staying in work and reducing absenteeism • independence for carers • reduction in social costs • increased tax revenue Symptoms of MS, including the emotional and physical impact of MS relapses, have a significant effect on people's ability to care for families and to carry out paid employment. The restriction of this ability during a relapse is of great concern and importance to people with MS. Research has shown that 37 per cent of people in paid employment take more than two weeks off work during a relapse. This evidence is backed up by the Work Foundation Report which found that on average 37 per cent of people with 'mild' MS are working and many more have had to change or quit their jobs due to the fluctuating nature of their MS . It also reported that 44 per cent of people with MS retire early, in comparison with the 35 per cent European average, and up to 80 per cent of people with MS retire within 15 years of diagnosis, severely shortening the working lives of young adults. Teriflunomide offers the potential for many people to continue working and to contribute to society. Current first-line options, either injections or infusions, can severely restrict people in what they can do, and force affected individuals to reduce their working hours or stop employment altogether. Enabling a person to live more independently, experience fewer relapses and require less care and support would improve their lives as well as their carers'. The Work Foundation report found that 'Professional careers of 57 per cent of relatives are adversely affected by MS of a family member' . The MS Society believes that a .	Comments noted. Please note that the appraisal accounted for the disutility of carers (see FAD section 4.17). It is stated, however, in the 2008 NICE Guide to the Methods of Technology Appraisal (paragraph 5.2.7) that *"the perspective adopted on costs should be that of the NHS and PSS. Technologies for which a substantial proportion of the costs (or cost savings) are expected to be incurred outside of the NHS and PSS, or which are associated with significant non-resource effects other than health, should be identified during the scoping stage of an appraisal. In these exceptional circumstances, information on costs to other government bodies, when these are not reflected in HRQL measures, may be reported separately from the reference-case analysis."*

Consultee	Comment	Response
MS Society	wider view must be taken when assessing the cost and benefits of teriflunomide. **5. Cost-effectiveness** We believe teriflunomide should be considered a cost-effective treatment for the following reasons: • We understand a Patient Access Scheme (PAS) has been agreed. Given discounts elsewhere, it seems reasonable to assume that the PAS is likely to bring the cost of teriflunomide in line with those medicines considered part of the MS Risk Sharing Scheme (RSS). • Compared with Copaxone, Avonex, Rebif and Betaferon, teriflunomide not only has similar (slightly better) efficacy, but all the benefits of oral delivery, making it the treatment of choice for many people with MS. As recognised by NICE, 'teriflunomide dominated the blended comparator in the base case… it was less expensive and more effective' (3.16, page 16). Given teriflunomide's potential to improve health outcomes without placing a greater burden on the tax payer or the NHS, we believe it would be perverse not to provide this medicine on the NHS. **Final comments** While the MS Society believes that there is sufficient evidence for the Committee to recommend the use of teriflunomide, we urge the manufacturer to meet NICE's requests for further clarification and analyses in time for the second Appraisal Committee meeting. If the Committee accepts that teriflunomide is at least as effective as current options, given the benefits to patients, the innovative nature of the treatment and its cost effectiveness would logically lead the appraisal to reach a positive outcome for people with MS.	Comments noted. The Committee concluded that teriflunomide could be considered an effective use of NHS resources for treating adults with relapsing–remitting multiple sclerosis for whom beta interferons and glatiramer acetate would otherwise be considered as treatment options, section 4.23 of FAD. Teriflunomide is recommended as an option for treating RRMS see section 1.

Consultee	Comment	Response
Association of British Neurologists and endorsed by the Royal College of Physicians	Thank you for the opportunity to respond to this report. Please see below for comments from the Association of British Neurologists. **1) Has all of the relevant evidence been taken into account?** We note the request for pairwise comparison and consideration of pre-2000 trial evidence. Otherwise, we believe all relevant evidence has been taken into account. **2) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes. **3) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The preliminary recommendations provide a sound and suitable basis for drafting the final guidance document as far as they go, but not a sufficient one. Although all the evidence we believe has been considered, we do not believe certain aspects have been given sufficient weighting in that consideration. Specifically, insufficient account has been taken first of the very substantial beneficial impact of an oral drug; and secondly of the unpredictability of drug failure with respect to DMTs in MS - i.e., even though the potency at a population level of teriflunomide appears not significantly greater than the interferons or glatiramer, we would still anticipate there will be patients who fail on conventional DMTs but respond to teriflunomide. Therefore on balance the ABN firmly believes that teriflunomide should be available to specialist prescribers for relapsing remitting MS. **4) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No.	Comments noted. The Committee concluded that teriflunomide could be considered an effective use of NHS resources for treating adults with relapsing–remitting multiple sclerosis for whom beta interferons and glatiramer acetate would otherwise be considered as treatment options, section 4.23 of FAD.

Consultee	Comment	Response
MS Trust	Please find below comments from the MS Trust in relation to the Appraisal Consultation Document (ACD) for teriflunomide, published in September 2013. The ACD states that the Appraisal Committee is minded not to recommend teriflunomide for the treatment of relapsing-remitting multiple sclerosis (MS). Our submission will address the following areas, as set out in the ACD, namely: a) Has all of the relevant evidence been taken into account? b) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? c) Are the provisional recommendations sound and a suitable basis for guidance to the NHS? d) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? We do not believe that there are any points relating to item D. All our points relate to the first three items for consideration. 1. The MS Trust wishes to make a general comment pertaining to the composition of the NICE Appraisal Committee. From the list of Appraisal Committee members who were involved in the teriflunomide review, it does not appear that there was anyone with specific neurological expertise. This is regrettable when discussing a complex condition such as multiple sclerosis (MS). We recognise that there were clinical experts present at the Committee meeting in September 2013, but continue to believe that this was insufficient input to ensure that all relevant clinical issues were identified and the clinical context was adequately described and therefore taken into consideration. 2. The MS Trust is very disappointed that the Committee is minded not to recommend teriflunomide for adults with relapsing-remitting multiple sclerosis. Our interpretation of the ACD is that the Committee's concerns centre around manipulation of the economic model which generated ICERs of between £6000 to £107,000 per QALY gained compared with glatiramer acetate. The committee has presented a series of technical questions for the manufacturer but has not been clear about the implications of the results of the additional analyses or what further evidence this is expected to provide. While we recognise the importance of establishing cost effectiveness for a new treatment, we feel that the appraisal process has been dominated by a very technical analysis of the economic model. This gives little opportunity for stakeholders with limited expertise in health economics to be able to participate and challenge assumptions. There is a danger of the appraisal process being consumed by hypothetical manipulation of the mathematical model and disconnected from the practical reality of clinical practice. The ACD acknowledges that "teriflunomide was clinically effective in reducing relapse rates compared with placebo, and that it may have a beneficial impact on accumulation of disability". Furthermore, the ACD states that "teriflunomide dominated the blended comparator in the base case…that is, it was less expensive and more effective". On the face of that evidence, that the drug is effective and cost-effective, that is has a positive effect on health outcomes and delivers value for the health service, it seems perverse that NICE would not recommend the drug for use in the NHS.	Comment noted. The area of speciality of physicians is not a prerequisite to standing as a Committee member. We ask for nominations of clinical specialists and patient experts and the chair will consider these applications with a view on who will be best placed to advise the committee. Please see the terms of reference for further information on the Appraisal Committee. Following the submission of further economic evidence from the manufacturer and consideration by Committee, teriflunomide has been recommended as an option for treating RRMS see section 1 of the FAD.

Consultee	Comment	Response
MS Trust	3. People with relapsing-remitting multiple sclerosis currently have very limited treatment options. The committee heard from both clinical and patient experts about the importance of access to a range of medicines, particularly for those who are unable to tolerate current treatments which are associated with significant side effects as well as injection site reactions. Despite the overall efficacy of current treatments for preventing MS relapses, any one of them can simply fail to work in a particular patient, or cause debilitating side effects. Clinicians lack tools to predict who would respond well to a specific therapy. Four of the five current first line treatments (Avonex, Betaferon, Extavia and Rebif) have the same mechanism of action. If a patient fails to respond to one of these drugs or develops side effects, glatiramer acetate is the only alternative treatment with a different mechanism of action. All of the current first line treatments are self-injected. Overwhelmingly, an oral route of administration is seen as a real benefit by people with MS. Through supporting people who are taking the current first line treatments, the MS Trust is aware that the requirement for long-term injections places a burden on them and in some cases leads to a decision not to start treatment, delays initiating treatment or results in reduced adherence. Self-injecting is painful, results in anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; and imposes restrictions on a number of aspects of general living. Uniquely, teriflunomide is taken as a tablet, it acts in a different way to the current disease modifying drug therapies, and has a different profile of side effects. It will significantly alter the range of treatments available to people with relapsing-remitting MS, providing a genuine alternative to the current therapies.	Comment noted. 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 see section 4.21 of FAD.
	4. There is no clinical evidence for treatment waning. Treatment waning was introduced by the manufacturer during the fingolimod appraisal (TA254). The manufacturer carried out a sensitivity analysis on their economic model to see what would happen if there was a hypothetical treatment waning and, not surprisingly, the ICER increased. The concept of treatment waning is without precedent in previous MS NICE appraisals. While we acknowledge that it is difficult to extrapolate two year clinical trial data to long term treatment, we wish to emphasise that there is no clinical evidence to support loss of efficacy. Moreover, there is no evidence to justify the arbitrary choice of 25% loss of efficacy at 2 years and 50% loss of efficacy at 5 years. Can the ERG or Committee explain why these levels, and not alternatives, should have been chosen? Treatment waning is hypothetical, is being used to test the responsiveness of a mathematical model and is not based on clinical observation. The ACD states (4.15, p39) "The Committee heard from the clinical specialists that they could not be confident that the treatment effect would not wane." This is a reasonable, professionally cautious response to the Committee's question. However, this is a leading question; what it does not make clear is the converse is equally true - that clinical specialists could not be confident that treatment effect would wane.	Comment noted. 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. See FAD section 4.18.

Consultee	Comment	Response
MS Trust	5. The MS Trust agrees with Committee's conclusion that teriflunomide has efficacy equivalent to current first line treatments, and we do not anticipate it being used as an alternative to fingolimod or natalizumab, although these were listed as comparators in the final scope. As stated in the ACD, clinical specialists considered that in clinical practice, teriflunomide would be viewed as a first line treatment option alongside glatiramer acetate and the beta interferons in line with ABN guidelines. The ACD states (4.2, p32) "teriflunomide…would be stopped if the person's condition converted to secondary progressive multiple sclerosis, or reached EDSS state 7." We would like to stress that this is not as clear cut as stated; the ABN guideline acknowledges the difficulty of identifying when treatment is no longer of benefit for an individual patient and concludes that it is not feasible to have mandatory stopping criteria that apply in all cases.	Comment noted. See section 1 of the FAD. The Committee recognised that conversion to secondary progressive disease or reaching EDSS 7 is often realised retrospectively (see FAD 4.3)
	6. With respect to treatment sequencing, we wish to stress that there is no treatment pathway in place for disease modifying treatments and it is not within the scope of the current appraisal to be making assumptions on sequence or escalation of treatments. The manufacturer explored hypothetical treatment sequencing in their submission to test their economic model. Manufacturer provided evidence for: • teriflunomide → 2→3 • blended comp → 2→3 where 2 or 3 could be blended comparator, fingolimod, natalizumab or best supportive care. The Committee has now asked for further combinations "reflecting UK clinical practice" (1.2, p4). We question whether these particular combinations reflect realistic sequences. • teriflunomide →□ Rebif→ □ fingolimod - vs - Rebif →□ fingolimod → □ nothing • teriflunomide→ □ Rebif→ □ GA - vs - Rebif →□ GA → □ nothing In UK clinical practice, switching or escalating treatments results from an individual's intolerable side effects or sub-optimal response to an initial treatment. An economic model cannot capture the benefit to the individual achieved by switching to an effective treatment. This reflects an urgent need within the UK for a much broader range of treatment options. As it is impossible to prognosticate for an individual, there is a need for flexibility to allow both clinician and patient to select a treatment that is both tolerable and effective for that person.	Comment noted. 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. However, the Committee concluded that the analysis of individual drugs (without a sequence) was basis for decision-making in this appraisal See FAD section 4.20
	7. The innovative nature of oral route of administration is acknowledged in the ACD, in fact the Committee considered that additional QoL benefits were not fully captured in the QALY (4.1, p30 and 4.21, p44). However, this aspect seems to have been overwhelmed by mathematical modelling. Those patients who don't tolerate the first line treatments face particularly challenging choices. An oral therapy such as teriflunomide would offer a real alternative for patients who otherwise may face the prospect of treatment withdrawal and consequent return of the pre-treatment rate of relapse and risk of axonal damage with increasing and irreversible disability, with all the associated individual and health service burdens.	

Consultee	Comment	Response
MS Trust	8. The MS Trust is confident that the Committee understands the serious nature of a diagnosis of MS and the impact of the condition on an individual's ability to remain in work and maintain independence and quality of life. What is less clear is whether a full account has been taken of the negative impact of a relapse on the person with MS or the real cost of a relapse. There are significant health-care related costs of even a single relapse, but additionally there are broader costs in terms of lost income for the person with MS and also potentially for informal carers who need to provide care and support during the disabling period of relapse. No less significantly there are physical and emotional costs to the person with MS. **Conclusion** Research evidence demonstrates the importance of active, early treatment of relapsing-remitting MS to prevent axonal damage and avoid irreversible disability. The EMA has licensed teriflunomide because it is an effective, safe drug for people with MS who have very few available treatment options. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long-term benefits of treatment. People with MS in the UK are at risk of lagging even further behind other developed countries in their access to licensed drugs. The MS Trust encourages the Committee to recognise that teriflunomide would be an important addition to the small range of available disease modifying therapies for MS. As with other disease modifying therapies, teriflunomide should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by specialist MS nurses.	Comment noted. The cost of each relapse, and the associated disutility was accounted for in the modelling, with different costs applied for relapses which did or did not require hospitalisation. In addition the impact on carers was accounted for by including a carer disutility (see FAD 4.17).

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Multiple Sclerosis Society of Great Britain and Northern Ireland	Many thanks for inviting me to comment on this recent STA. I attended as a clinical expert nominated by the Multiple Sclerosis Society of Great Britain and Northern Ireland. I commend the committee for the work that has gone into this STA and detailed analysis and careful thoughtful judgement. I have confined my comments to the questions specifically raised in your email. **Has all of the relevant evidence been taken into account?** Yes I believe so. I was particularly pleased that a person with multiple sclerosis on terifluonimide was able to attend the committee meeting and provide their perspective. To my mind terifluonimide's strength as a potential agent for the treatment of relapsing-remitting multiple sclerosis lies in its ease of administration (no oral first line therapy currently exists) and the difference this can make to a person's life. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes. The data appears to show that terifluonimide is not inferior in efficacy to standard first line treatment of multiple sclerosis (beta-interferon) and with the proposed patient access scheme is available at comparable cost. I am unsure why a request has been made to model for a treatment waning effect as to my knowledge there is no evidence to suggest this occurs.	Comment noted. 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 section 4.21 of the FAD. Comment noted. 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. See FAD section 4.18.

Nominating organisation	Comment	Response
Multiple Sclerosis Society of Great Britain and Northern Ireland	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** I believe the provisional recommendations are a thoughtful and considered judgement and take into account certain issues regarding long term modelling of multiple sclerosis as a disease entity and the fact that from an efficacy viewpoint terifluonimide appears not to confer any advantage in comparison to already available therapies (beta-interferon, glatiramer acetate). I have sympathy with the above view but strongly feel that terifluonimide should be made available on the NHS because it has genuine innovation as an oral therapy. It is clear to me as a practising neurologist treating many people with relapsing-remitting multiple sclerosis that the currently available options which are all injectable have the potential to damage skin, stigmatise by the visibility of the administration and in some cause great anxiety and discomfort. This has led to some people who would be eligible for therapy choosing not to treat their multiple sclerosis which has been detrimental to their long term care. Although in an ideal world one would wish terifluonimide to have greater efficacy and have a shorter wash out period regarding planning for pregnancy this in my opinion should not prevent its approval. The availability of a first line oral therapy will I believe make a genuine difference to a number of people's lives and as long as prescribing is confined to specialist units with neurologists with sufficient expertise in multiple sclerosis and integration with specialist nurse services then suitable counselling and checks will be put in place to minimise inappropriate prescribing and avoid use of the drug when pregnancy is planned.	Comment noted. 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 section 4.21 of the FAD. The Committee went on to conclude that teriflunomide could be considered an effective use of NHS resources for treating adults with relapsing–remitting multiple sclerosis for whom beta interferons and glatiramer acetate would otherwise be considered as treatment options, section 4.23 of FAD.

Nominating organisation	Comment	Response
MS Society	Further to the public response by the MS Society, I would like to add some additional comments based on the additional information I was sent on a confidential basis as a patient expert. In the MS Society response there is an assumption that a fairly typical discount for MS patient access schemes of around [redacted] has been applied. That would put teriflunomide broadly into the price spectrum for the range of current first line treatments available through the risk sharing scheme. [redacted] People with MS would benefit from an additional treatment option, which scores highly on innovation and which [redacted]	Comments noted.

Comments received from commentators

Commentator	Comment	Response

Novartis	Novartis would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to respond to the draft appraisal consultation document (ACD) for teriflunomide. Please note that we will respond to the manufacturer's model in a separate email. Our review of the ACD document highlights some significant concerns regarding the inclusion of fingolimod as a comparator. Furthermore, we wish to raise important considerations for the economic and clinical analyses of fingolimod and teriflunomide that have been conducted as part of the appraisal to this point. We believe it is vital to evaluate teriflunomide in a scientifically accurate manner when comparing to other disease modifying therapies (DMTs), in order to ensure that multiple sclerosis patients have access to the most clinically- and cost-effective therapies.
	Our key areas of concern are:
	• The use of fingolimod as a comparator, given the clinical expert opinion was clear that teriflunomide would not be used in the more aggressive forms of the disease, such as highly active RRMS (the population for which fingolimod is indicated and reimbursed (TA254))
	• The cost and clinical effectiveness of teriflunomide has been compared to fingolimod throughout the ACD assuming that fingolimod is used inappropriately in a broad MS population, including in 1st-line
	• We would like to remind the committee that in TA254 the use of fingolimod is limited to patients in highly active relapsing remitting multiple sclerosis (RRMS) following beta interferon treatment. Where this sub-group analysis has been conducted, the strength of the conclusions that can be drawn is weak, given the small number of teriflunomide patients
	• In the event that fingolimod is used as a comparator, our major concerns are:
	  o The inclusion by the Evidence Review Group (ERG) of the patient access scheme (PAS) for teriflunomide but not for fingolimod, without any sensitivity analyses to mimic the impact of fingolimod's PAS
	  o The use of a cost-effectiveness model that incurs greater benefits for therapies that have a higher discontinuation rate, which favours teriflunomide over fingolimod
	  o The use in the cost-effectiveness model of disability data based on 3-month rather than the EMA-recommended 6-month sustained disability progression
	Summary of suggested actions for the Committee:
	• We believe that fingolimod should be removed as a comparator to teriflunomide in relapsing-remitting multiple sclerosis (RRMS) in light of the fact that fingolimod holds a marketing authorisation and recommendation from NICE (TA254) for use in highly active RRMS patients following beta interferon treatment. This is a very small subset of the teriflunomide marketing authorisation and one for which clinical experts do not believe that teriflunomide would be used. Comparison of fingolimod in a first-line position is inappropriate and the data is insufficient to allow a reliable comparison in the exact indication for which fingolimod is licensed.
		Comments noted. 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 See FAD sections 4.9 and 4.23

Commentator	Comment	Response
Novartis	• If fingolimod is to be presented as a comparator, then consideration should be given to the points of concern outlined above The structure of our full response is as follows: Section A: Main Comments on the ACD – *in this section we highlight our main concerns with the manufacturer's submission and the evidence presented in the ACD* Section B: Additional Comments on the ACD – *in this section we highlight all additional concerns surrounding the analyses and discussions that have been presented within the ACD* Section C: Consistency with Previous Technology Appraisals – *in this section we highlight any issues relating to maintenance of consistency between technology appraisals in this disease area, where appropriate* **<u>Section A: Main Comments on the ACD</u>** 1. **Comparisons Reported in the ACD** Fingolimod holds a marketing authorisation and recommendation from NICE (TA254) for use in highly active RRMS patients following beta interferon treatment, which is a very small subset of the teriflunomide marketing authorisation. It is not appropriate to compare teriflunomide and fingolimod in this sub-population for whom the marketing authorisations overlap, due to the following reasons: • Clinical experts considered that teriflunomide would be most appropriately positioned as a first-line therapy option for what they described as 'conventional' patients. We interpret this to mean patients with RRMS, rather than a highly active or rapidly-evolving severe form; this is not the population for which fingolimod is licensed. • Clinical experts noted that they would expect limited, if any, role for teriflunomide in the more active forms of the disease (ie. highly-active RRMS) for which fingolimod is licensed and recommended by NICE • Given the clinical pathway and the data limitations, the manufacturer of teriflunomide (Genzyme) stated that they did not consider fingolimod as an appropriate comparator The comparison of teriflunomide with fingolimod presented in the ACD is not based on the sub-population defined by the fingolimod marketing authorisation and recommendation from NICE (TA254) and is therefore inappropriate. Specifically, our main concerns with this comparison are as follows: a) <u>First-line Use of Fingolimod</u> The cost and clinical effectiveness of teriflunomide has been compared to fingolimod throughout the ACD assuming that fingolimod is used as a first-line therapy. This comparison with fingolimod as a first-line agent is outside both the marketing authorisation for fingolimod and the NICE recommendation in TA254. Analysis of data from a major homecare supplier, as	Comments noted. 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 See FAD sections 4.9 and 4.23.

Commentator	Comment	Response
Novartis	of 4th October 2013, offers suitable data for analysis in 240 out of 381 active patients. In the group of 240 patients there is evidence of prior treatment with a beta interferon or glatiramer acetate. Therefore, a comparison with fingolimod based on use as first-line therapy is unlikely to reflect real-world UK practice. b) <u>Subgroup Considerations</u> We believe that the manufacturer's base case mixed treatment comparison is not relevant due to the fact that it does not consider the specific population of patients with highly active RRMS in which fingolimod is currently used, in accordance with the licensed indication and NICE recommendation (TA254) of fingolimod. The Evidence Review Group (ERG) used the comparison of the whole trial populations in their economic analysis, which is inappropriate, and additionally compared teriflunomide to fingolimod in first line position (see section 1a above). c) <u>Data Limitations</u> Although the manufacturer did present a mixed treatment comparison that utilised subgroup analyses of highly active RRMS, we note that all stakeholders (Genzyme, the ERG and the NICE Committee) agree that this subgroup analysis is unreliable due to very small patient numbers and therefore no meaningful conclusions can be drawn from it. Furthermore, this analysis was conducted based on a first-line positioning (see section 1a). Given the inappropriate nature of the first-line comparison, coupled with this severe lack of reliability, it seems incorrect to include the results of this subgroup analysis within the ACD. Inclusion of inappropriate comparisons may generate false perceptions of the cost effectiveness of fingolimod in the clinical community. This could lead to inappropriate clinical decision-making, which could potentially be directly detrimental to patients. This analysis should therefore be removed from the appraisal report. <u>Conclusion on Comparisons Reported in the ACD</u> To present a comparative analysis for teriflunomide and fingolimod as first-line agents in either the general MS population or in a highly active RRMS population based on unreliable subgroup data seems inappropriate from both a clinical and statistical perspective. **We therefore believe that the current conclusions on cost-effectiveness relating to fingolimod are inappropriate and misleading, and should therefore be withdrawn from the appraisal report.** If it is not possible to robustly compare teriflunomide and fingolimod within the latter's marketing authorisation and NICE recommendation in the manufacturers' model then fingolimod should be removed as a comparator from this analysis. **All reference to fingolimod being dominated economically and clinically by teriflunomide should be removed as these findings are not supported by the clinical evidence and the accuracy of these claims cannot be supported reliably by the model.**	Comments noted. 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 See FAD sections 4.9 and 4.23.

Commentator	Comment	Response
Novartis	**2. Comparisons Requested in the ACD** Novartis note that the NICE Committee has specifically requested Genzyme to perform the following pairwise comparison, which the Committee supposed to reflect 'plausible treatment sequencing, reflecting UK clinical practice': *teriflunomide, Rebif-44 (interferon beta-1a, 44 micrograms) and fingolimod compared with Rebif-44, fingolimod and no disease-modifying therapy* Where RRMS patients can be identified as having an aggressive form of MS at diagnosis, it is unlikely that clinicians would start prescribing with teriflunomide, as it was heard from the clinical experts at the committee meeting that they would expect limited, if any, role for teriflunomide in the more active forms of the disease. This would make the above treatment sequence involving teriflunomide unlikely in clinical practice, and therefore the comparison requested by the NICE Committee is inappropriate for these highly active patients. In the case where highly active disease is diagnosed after first-line treatment, the above sequencing with the use of teriflunomide first line could be deemed appropriate. However, in this case there is a lack of data to make this comparison of treatment sequences. Furthermore, it would be inappropriate to use the whole trial population from teriflunomide to represent patients with highly active disease, as it would be expected that patients with highly active disease would discontinue teriflunomide at a faster rate than seen for the whole population, and also be subject to greater relapse rates. Given the lack of data for treatments in the specific requested sequences and the unreliable nature of the subgroup analysis for teriflunomide in highly active patients (see Section 1b), the data does not allow for a robust and reliable comparison of the sequences outlined above. Therefore a fair and accurate comparison of the scenarios involving teriflunomide and fingolimod described above is impossible with the currently available data and should not be requested. **<u>Section B: Additional Comments on the ACD</u>** For the reasons outlined above, we feel that the inclusion of fingolimod as a comparator in this appraisal is inappropriate and would request that all reference to fingolimod as a comparator be removed from the ACD. However, given that the current draft of the ACD does consider fingolimod as a comparator and presents comparative analyses of clinical and cost-effectiveness of teriflunomide and fingolimod, we feel that it is necessary to highlight inaccuracies and areas of concern that we have with these analyses, in addition to the concerns already raised by the ERG and the NICE Committee. a) <u>Concern over the ERG's Economic Analysis in Patients with Highly Active RRMS</u> As part of their review, the ERG used a corrected version of the manufacturer's model to conduct a cost-effectiveness analysis of teriflunomide versus fingolimod in people with highly active RRMS [Section 3.42].	Comments noted. 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 See FAD sections 4.9 and 4.23.

<table>
<tr><th>Commentator</th><th>Comment</th><th>Response</th></tr>
<tr><td>Novartis</td><td>
In conducting this analysis, the ACD notes that ‘the patient access scheme price for fingolimod was not applied’. In contrast, the patient access scheme (PAS) for teriflunomide is included in this analysis, for which conclusions regarding relative QALYs and costs with teriflunomide and fingolimod are presented.

Given that fingolimod is subject to a PAS that acts to reduce its price at reimbursement, it is not a reasonable approach to form conclusions regarding the relative cost of teriflunomide and fingolimod based on an analysis in which the PAS was not consistently applied for fingolimod. We accept that the PAS for fingolimod is subject to a confidentiality agreement and hence the exact details of the reduction in cost of fingolimod are not known to the ERG. However, given that the manufacturer of teriflunomide applied a range of discounts to mimic the fingolimod PAS as part of their sensitivity analyses [Section 3.15], we cannot understand why a similar approach was not presented by the ERG. To present concluding statements on the relative costs of teriflunomide and fingolimod based on an analysis which is unrepresentative of the nature of the reimbursement for fingolimod in reality is entirely inappropriate.

b) <u>Disability Progression</u>

Within the ACD, the ERG have commented that an analysis based on 6-month SAD data, rather than 3-month SAD data, would be preferable because there remains a possibility of recovery from disability at 3 months [Section 3.24]. The ACD notes that the Committee heard from clinical specialists that 6-month SAD is a more appropriate outcome than 3-month SAD and that this is also the preference of the European Medicines Agency as outlined in its draft guidelines for the clinical investigation of medicinal products for the treatment of multiple sclerosis [Section 4.5]. In addition, an expert panel also supports this recommendation.(1) There is therefore a comprehensive case to support the use of 6-month SAD data, rather than 3-month SAD data, where possible.

Although we fully understand that 6-month SAD data is not available for all comparators, and hence analyses using 3-month SAD may have been the most appropriate to present more generally, we wish it to be noted that 6-month SAD data is available for both teriflunomide and fingolimod (see Table 1).(2, 3)

<u>Table 1: 24-week sustained disability progression at 24 months</u>
<table>
<tr><th></th><th>Teriflunomide(3)</th><th>Fingolimod(2)</th></tr>
<tr><th></th><th>14mg</th><th>0.5 mg</th></tr>
<tr><td>Reduced risk over placebo</td><td>25.1%</td><td>37%</td></tr>
<tr><td>P value</td><td>0.1259</td><td>0.01</td></tr>
</table>
</td><td>Comments noted. 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 See FAD sections 4.9 and 4.23.</td></tr>
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Commentator	Comment	Response
Novartis	The Committee concluded that 'in light of the lack of 6-month SAD data available, 3-month SAD should be considered' [Section 4.5]. However, this conclusion does not apply to the comparison of fingolimod and teriflunomide, for which 6-month SAD data is available for the intention to treat (ITT) population. Although a comparison of the ITT populations rather than of the highly active subgroup of patients is not specifically relevant to the decision problem, as this comparison has been performed and presented in the ACD for the 3-month progression outcome, we feel it should also be presented for the more clinically robust 6-month outcome for teriflunomide versus fingolimod. We would therefore question why this analysis was not performed and would politely request that the Committee considers the potential implications of such an analysis based on 6-month SAD data in terms of the relative clinical- and cost-effectiveness of the two therapies. This is an especially important consideration, given that the Committee notes that disease progression estimated using 3-month SAD is a key driver of the manufacturer's model [Section 4.11]. The use of the more appropriate 6-month SAD data in the comparison of fingolimod and teriflunomide that is presented in the ACD would hence be expected to be influential in providing a more accurate estimate of the relative cost-effectiveness of the two treatments. There is reason to expect that a comparison of teriflunomide and fingolimod based on 6-month SAD data would be less favourable to teriflunomide in terms of the incremental cost-effectiveness ratio (ICER) than the comparison conducted within the manufacturer's submission based on 3-month SAD data. This is because fingolimod has demonstrated significant improvements versus placebo in terms of 6-month progression, whilst the 6-month disability progression data for teriflunomide shows only numerical, but non-significant, improvements for teriflunomide compared to placebo (see Table 1).(2, 3) Given that 6-month progression data is more clinically relevant we feel that it is important to highlight these results and their potential impact upon the cost effectiveness of the two treatments. c) <u>Adherence Rates</u> We are concerned about the impact that adherence rates have on the cost-effectiveness analysis of teriflunomide in comparison to fingolimod. As noted by the ERG, in the manufacturer's model a treatment becomes more cost-effective if more patients stop treatment; this is a counter-intuitive feature of the model [Section 3.41]. This feature means that a therapy with higher adherence rates, which is likely to represent an important clinical factor in terms of maximising treatment benefit, is disadvantaged in the cost-effectiveness analysis.(4) This situation applies to the comparison of teriflunomide and fingolimod, since there is evidence that discontinuation rates between teriflunomide and fingolimod could be different, with potentially higher discontinuation rates for teriflunomide. In the FREEDOMS I trial of oral fingolimod, 19% of patients receiving the licensed 0.5 mg dose discontinued the study drug.(2) For teriflunomide, the rate of discontinuation of the study drug in the TEMSO trial was higher, at 26.5%.(5) Further support for high adherence rates with fingolimod is provided from a study addition, results from this study report that 98.8% of fingolimod patients found their medication easy to take.(7) We feel that the benefits of higher adherence are not captured by the economic model and that this important point warrants acknowledgement by the appraisal Committee. For informative purposes, a sensitivity analysis could be run that investigates the impact of setting the	Comments noted. 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 See FAD sections 4.9 and 4.23.

Commentator	Comment	Response
Novartis	of real-world clinical practice use of fingolimod (PANGAEA). This study reported that the discontinuation rate amongst 2239 patients treated with fingolimod was only 11%.(6) In addition, results from this study report that 98.8% of fingolimod patients found their medication easy to take.(7) We feel that the benefits of higher adherence are not captured by the economic model and that this important point warrants acknowledgement by the appraisal Committee. For informative purposes, a sensitivity analysis could be run that investigates the impact of setting the discontinuation rates equal for teriflunomide and fingolimod. d) <u>Long-term Outcomes</u> Assumptions for long-term treatment effect are often applied equally across treatments due to an absence of long-term data. However, in reality, treatments may not be equivalent in terms of their efficacy in providing long-term outcome benefits. We are concerned that there does not appear to be any discussion on this in the ACD, as it may impact the relative cost-effectiveness of treatments – if a treatment is able to achieve outcomes for which the benefits influence disease in the long-term, then this may impact treatment and care requirements (including costs) in future years. There is evidence that fingolimod is able to provide benefits in terms of long-term outcomes; for example fingolimod has shown consistent reductions in brain volume loss across three large Phase III studies and over time. A significant effect is seen as early as 6 months in the placebo-controlled studies (FREEDOMS; FREEDOMS II)(8) and there is data to support that outcomes for reductions in brain volume loss with fingolimod are sustained even after 48 months of follow-up.(9, 10) Brain volume loss has been shown to generally correlate with disability progression.(11, 12) This loss already occurs very early in the disease and brain volume loss has been shown to predict the conversion from clinically isolated syndrome to clinically definite MS.(13) Importantly, whole brain volume loss also predicts 10-year disability.(14) This therefore strongly implies that the brain volume loss outcomes demonstrated for fingolimod support the sustained effectiveness of fingolimod in the long-term. In contrast, we are not aware of any such similar demonstration of the effectiveness of teriflunomide in terms of long-term outcomes. As such, an assumption of equivalence between fingolimod and teriflunomide in terms of long-term outcomes may not represent an accurate representation of the real clinical situation and may lead to false and unfair conclusions regarding the cost-effectiveness of teriflunomide versus fingolimod. We would therefore politely request that there is acknowledgement that this assumption has been made and that this may not be accurate, given that there is long-term data to support fingolimod but the same such data is not available for teriflunomide.	Comments noted. 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 See FAD sections 4.9 and 4.23.

Commentator	Comment	Response
Novartis	**<u>Section C: Consistency with Previous Technology Appraisals</u>** **Best Supportive Care** Although we acknowledge that the ERG and the Committee concluded that use of a blended comparator in the manufacturer's model was inappropriate (Section 3.34 and Section 4.10), we feel that it is nonetheless important to highlight an inconsistency between the approach to the blended comparator taken in the fingolimod appraisal (TA254) and in this appraisal for teriflunomide. As part of the fingolimod appraisal, the NICE Committee requested that the blended comparator that was used included best supportive care amongst its composite treatments. In contrast, we note that for the teriflunomide appraisal the blended comparator used in the manufacturer's economic analysis and in the subsequent analyses conducted by the ERG, does not include best supportive care [Section 3.13]. Best supportive care represents a low cost option and so the inclusion of this therapy option as part of a blended comparator would be expected to improve the cost-effectiveness of the blended comparator therapy. We therefore believe that there is an inconsistency between the methods used in the fingolimod appraisal and in this teriflunomide appraisal as regards the blended comparator, and that this inconsistency unfairly disfavours fingolimod relative to teriflunomide in terms of their respective cost-effective analyses against the blended comparator. **Conclusion** In conclusion, we believe that the inclusion of fingolimod as a comparator to teriflunomide in this appraisal is inappropriate on the basis of both clinical and statistical considerations. Fingolimod should therefore be removed from consideration as a comparator in this appraisal. Where comparisons of teriflunomide and fingolimod have been made, we have a number of significant concerns regarding appropriateness of the analyses conducted and the conclusions that can be drawn from them. These concerns are based on the limited data for teriflunomide in the highly active RRMS population for which fingolimod is licensed and reimbursed, the lack of consideration of the more clinically robust 6-month SAD data within the appraisal and the conclusions regarding fingolimod that have been drawn from an economic model that unfairly disadvantages fingolimod in a number of ways, as outlined above.	Comment noted. The Committee agreed that using a blended comparator was inappropriate, noting the ERGs reservations that it hid effects of individual treatment changes in the model (see FAD section 3.34). The Committee agreed that the manufacturer's revised base case reflected the Committee's preferred analyses, that is, the results were presented incrementally for all comparators rather than using a blended comparator (see section 4.11) A fully incremental analysis is the preferred approach. Occasionally the Committee has considered it necessary to also consider blending of comparators appropriate. In this appraisal blending of comparators was not required for decision making.

Commentator	Comment	Response
Novartis	**<u>Impact of treatment discontinuation rates (critical point)</u>** **Description of problem** THE ERG report notes that “the probability of withdrawal has the potential to have an important and perverse effect on the ICER” (7.0 ERG report p87) since a higher discontinuation rate would be associated with a higher ICER. Table 36 in the ERG report is commercial in confidence but in the model a single discontinuation rate is used for all treatments except teriflunomide where the discontinuation rate is double that of other treatments. **Description of proposed amendment** We propose that the model should be re-run with the same discontinuation rate applied to all treatments as the base case. **Result of amended model or expected impact on the result (if applicable)** We re-ran the model to apply the same discontinuation rate for all comparator drugs (including BSC) comparing teriflunomide with a pooled comparator. This led to a doubling of the ICER which implies that the ERG’s comments on the perversity of the model are both accurate and relevant to the decision problem. We then compared teriflunomide with fingolimod alone using equivalent discontinuation rates and this led to a greater than 6 fold increase in the teriflunomide ICER. Given the uncertainty arising from discontinuation and the impact of this parameter on the ICER, this issue warrants considerable further analysis **<u>Monitoring costs attributable to fingolimod</u>** **Description of problem** On the “cost data” worksheet cells C69 and C63 it is unclear whether the neurology visits specified are nurse or physician visits. In cell G83 2 neurology visits are applied for “subsequent years”. In the 2012 model of fingolimod, 1 visit was applied to subsequent years and this frequency fits with common practice **Description of proposed amendment** Genzyme should clarify whether the neurology visits described are physician visits. The “subsequent years” cell for fingolimod neurology visits should be amended to 1 for parity with the previous model **Result of amended model or expected impact on the result (if applicable)** The model has been re-run with all subsequent year neurology appointments set to 1. This leads to a very small decrease in the teriflunomide ICER. We also re-ran the model with fingolimod neurology visits set to 1 and all other products set to 2. We were surprised to see that this led to no change in the deterministic results (to 6 decimal places) and potentially warrants further investigation.	Comments noted.

Commentator	Comment	Response
Novartis	**<u>Model parameters for PSA</u>** **Description of problem** On the "model parameters" worksheet cells G700 to G712 we note that a gamma distribution has been applied to the PSA for utility and disutility values. Since a gamma distribution ranges from zero to infinity and is not commonly applied to utility values **Description of proposed amendment** The gamma distribution could be replaced with a normal distribution to reflect more accurately the range of expected values or a robust rationale for the use of gamma distribution should be provided. **Result of amended model or expected impact on the result (if applicable)** We re-ran the model in 100 iterations, replacing the gamma distribution with a normal distribution for utilities (not for disutilities) and found that teriflunomide was dominated. The model may be highly sensitive to the distribution of utilities and this issue warrants further investigation.	Comments noted.
Merck Serono	Merck Serono is grateful for the opportunity to comment on the appraisal consultation document (ACD) for teriflunomide for treating relapsing forms of multiple sclerosis which we received on 11th September 2013. We have reviewed the ACD along with the manufacturer's submission. We acknowledge the views of the appraisal committee and support the case for additional and subsidiary analysis to be conducted in order to reduce the uncertainty around the clinical and cost effectiveness of teriflunomide, especially when compared to other available treatments. We also noted that adherence to oral medications was not considered in the economic analysis. This was presumably since this analysis draws its data from controlled trials where patients are followed up closely to ensure adherence to the treatment regimen. However, this does not reflect patient treatment in real life. This could possibly have significant impact on the clinical and cost effectiveness of any multiple sclerosis treatment. In light of this Merck Serono believe that an assumption for the level of patient adherence to teriflunomide treatment should be treated as an uncertainty and should be considered within the economic analysis.	Comments noted. No evidence on adherence was provided in this appraisal. The patient testimony in favour of oral treatment and avoiding injections was very strong (FAD section 4.1), and was understood by the Committee. Therefore exploration of the impact of adherence was not needed.

Commentator	Comment	Response
Biogen	Biogen Idec thanks NICE for the opportunity to review the Appraisal Consultation Document (ACD) for teriflunomide for treating relapsing forms of multiple sclerosis. Our comments are in relation to the robustness of the health economic model for teriflunomide. **MODEL STRUCTURE** The overall structure appears consistent with previous models used in previous NICE appraisals based on EDSS; however, we note that the structure does not allow for the regression of disability between EDSS states. Excluding regression will result in the patient population progressing rapidly to higher EDSS states and SPMS than it would be expected under real-world conditions. This has an impact on the reliability of the ICER of teriflunomide versus the comparator. **PATIENT POPULATIONS** Disability progression is the main driver of the model. There seems to be a discrepancy with the patient population selection used in the MTC vs. the teriflunomide group. The distribution of SPMS patients in the teriflunomide studies selected appear to have higher baseline EDSS scores compared to those utilized in the MTC. As a consequence patients might move more quickly into high EDSS scores in the teriflunomide group, thus enhancing teriflunomide's ability to demonstrate an impact on disability progression (as per comment above). This would therefore lead to an inaccurate cost-effective analysis. **MTC RESULTS** The hazard ratios and relative rates of relapses are difficult to interpret and threaten the face-validity of the model; for example, the hazard ratio for Betaferon is 1.21, with BSC 1.0. Particular attention should be placed into the results showing interferon1-b having worse clinical outcomes than BSC. Further, the MTC treatment effects do not appear to be consistent with the head-to-head studies available; e.g. TENERE. This threatens the predictive validity of the MTC.	Comment noted. The Committee agreed that EDSS regression should be incorporated in the model, and this was included in the manufacturer's revised base case (see FAD sections 4.15). Comment noted and raised at Committee. As above, the Committee agreed that EDSS regression should be incorporated in the model, and this was included in the manufacturer's revised base case (see FAD sections 4.15). Comment noted. The Committee acknowledged the limitations of the MTC presented by the manufacturer The Committee agreed that the 'all years' MTC adjusted for baseline relapse rates was appropriate (see FAD 4.7).

Commentator	Comment	Response
Biogen	**BLENDED COMPARATOR** As stated in section 3.13 of the NICE ACD report for teriflunomide, there appear to be two deviations in relation to NICE guidance regarding the use of Blended Comparators. The deviations were that the blended comparator was calculated as the weighted average of the clinical input parameters (e.g. mean relative rates) and secondly that the cost-utility was calculated on the basis of the UK market share data. Further the approach to use a simple weighted mean of each treatment outcome is methodologically flawed and does not reflect the use of individual products in the UK. Teriflunomide should be compared against comparators individually and the base case comparison should be versus the product most likely to be displaced. Throughout the model, simple assumptions on the weighting have been made without any regard to utilising best available evidence e.g. relative rate leading to hospitalization, annual all-cause withdrawal rate. This goes against the principles of evidence-based decision-making and severely compromises the validity of the model.	Comment noted. The Committee agreed that the manufacturer's revised base case reflected the Committee's preferred analyses, that is, the results were presented incrementally for all comparators rather than using a blended comparator (see section 4.11)
	ADVERSE EVENTS The adverse events rates unduly bias in favour of teriflunomide. Teriflunomide is associated with a very short list of adverse events (i.e. nausea, diarrhoea, hair-thinning) compared to the comparators. A comprehensive and transparent list of adverse events for teriflunomide should be provided and included in the MTC analyses by the manufacturer.	Comment noted. The Committee noted that the adverse events were not a key driver of the model and had only a small impact on the ICER (see FAD section 4.17).
	In addition, teriflunomide remains in the body for up to 2 years after patients stop treatment. The impact of the long half-life of teriflunomide on adverse event rates and subsequent costs was not explored in the model/submission -the SmPC recommends that women, who have previously taken teriflunomide, should have their levels checked prior to pregnancy to ensure plasma levels are below (above or below?) O.02mg/l, this requires long-term follow up of patients. It appears that the submission does not explore this scenario in any sensitivity analysis.	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 see section 4.10 of the FAD

Comments received from members of the public

No comments received