Response from Genzyme to the teriflunomide ACD sent to NICE on 9th October 2013.

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.

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.

- 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

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:
    - The inclusion criteria for TEMSO and TOWER studies related to EDSS score were 0 to 5.
    - Duration of the studies: two years for TEMSO and for TOWER a median study treatment duration of about 1.5 years.
    - 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

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 (%, % and % 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: 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 %, % and % 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 % and % 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 % 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.

- 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 % 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 %-% 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)

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:
  - 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.

  - 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 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.

  - 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 Genzyme in 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:

    - Page 18 "we anticipate that teriflunomide will be used in patients with RRMS who otherwise would receive beta-interferons or glatiramer acetate."

    - Page 25: "The positioning of teriflunomide is as an alternative to beta-interferons or glatiramer acetate"

    - 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."

    - 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]".

- 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."

- 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 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

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