National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Teriflunomide for treating relapsing forms of multiple sclerosis [ID548]

You are asked to check the ERG report from the Centre for Reviews and Dissemination and Centre for Health Economics to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **8 August 2013** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Accurate Summary of ERGs preferred cost effectiveness analysis

Description of problem	Description of proposed amendment	Justification for amendment
Wording on page 21 (first paragraph in Section 1.7) as follows: "The ERGs preferred analysis results in teriflunomide being dominated (ie. more costly and less effective) compared to glatiramer acetate using the non-PAS price and an ICER of £107,148 per QALY gained compared to glatiramer acetate using the PAS price."	"The ERGs preferred analysis results in teriflunomide being dominated (ie. more costly and less effective) compared to glatiramer acetate using the non-PAS price and an ICER of £107,148 per QALY gained compared to glatiramer acetate using the PAS price. Using the PAS price, teriflunomide dominates Rebif 44, Avonex and Betaferon and the blended comparator and Rebif 22 is more effective but is not cost effective compared to teriflunomide with an ICER of £917,667."	The suggested alternative wording is a factually accurate summary of the preferred analyses carried out by the ERG. The summary as it presently reads incorrectly suggests that the only analyses carried out by the ERG were against glatiramer acetate. In clinical practice it is anticipated (as shown in Table 56 page 117 of the report) that 77% of patients using teriflunomide would be using it in place of a drug other than glatiramer acetate.

Issue 2 Accurate description of the manufacturer's positioning of teriflunomide

Description of problem	Description of proposed amendment	Justification for amendment
Wording throughout the document of which the following on page 19 is an example: "The manufacturer has positioned teriflunomide as a first-line treatment to be used for patients that would otherwise take beta-interferons or glatiramer acetates."	We would suggest the following correction: "The manufacturer has positioned teriflunomide to be used for patients that would otherwise take beta-interferons or glatiramer acetates including first line use."	This is in line with the positioning that we included in our STA submission. For example on page 42 Section 2.5 of our STA submission we stated: "It is anticipated that teriflunomide will be used in RRMS where beta-interferons or glatiramer are currently prescribed. Teriflunomide provides an alternative option."

Other use of this wording is p18,21,68,69,89,104,114 (x3), 116,117,118,126,127,131		It is wrong to consider data presented by Genzyme in relation to exclusive use in first line positioning. It is appropriate to consider data presented by Genzyme as it relates to teriflunomide use in place of betaferons and glatiramer acetate which includes both first and second line use.

Issue 3 Accurate description of the rationale for a year 2000 cut-off for the manufacturer's base case MTC

Description of problem	Description of proposed amendment	Justification for amendment
Suggested changing this wording on page 16, paragraph 4, sentences 3 and 4: "The ERG has one major criticism which is of the decision to exclude pre-2000 trials from the base case analysis. In the opinion of the ERG some covariate analyses using the All Years network to control for potential confounders would have been more appropriate and would have avoided the loss of the placebo comparisons for the beta-interferons."	Suggested alternative wording: "The ERG has one major criticism which is of the decision to exclude pre-2000 trials from the base case analysis. The reason given for this restriction was that ARRs have fallen in clinical trials and hence older trials will have higher baseline rates than more recent trials. The cut off at the year 2000 was selected because of the introduction of the McDonald diagnostic criteria in 2000 to replace the Poser criteria. Compared with the Poser criteria, the McDonald criteria generally identify patients much earlier in the disease course, and with less frequent or severe symptoms; therefore, a change in MS diagnostic criteria may have considerable impact on the	This additional wording is taken from page 49 of the ERG report. It is important to consider the rationale for excluding pre 2000 studies given its' high impact on ICERs and state it up front as a contextual piece whenever this issue is discussed.

	baseline disease activity of the patient population under study. The publication of the CHAMPS study in 2001 was also cited as a reason for this restriction. This restriction was supported by Key Opinion Leaders consulted by the manufacturer and by a comparison of baseline relapse rates and treatment effects pre and post 2000. In the opinion of the ERG some covariate analyses using the All Years network to control for potential confounders would have been more appropriate and would have avoided the loss of the placebo comparisons for the beta-interferons.”	

Issue 4 Accurate description of highly active disease despite interferon use

Description of problem	Description of proposed amendment	Justification for amendment
Wording relating to highly active (HA) RRMS of which this is an example on page 13: “The manufacturer included an analysis of the subtypes RRMS: highly active (HA) …”	Suggested alternative wording: “The manufacturer included an analysis of the subtypes RRMS: highly active (HA) despite interferon use …”	Although there is some variation in use, for many clinicians (and almost exclusively within the literature), highly active RRMS would include both those with RES and HA disease despite interferon use. The wording presently used within the document has the potential to cause confusion since HA RRMS is used synonymously with HA disease despite interferon use (we recognise that some of this lack of precision in language is to be found also in our STA submission)

Issue 5 Accurate representation of the highly active subgroup analysis that can be carried out from the teriflunomide studies

Description of problem	Description of proposed amendment	Justification for amendment
Wording which we suggest needs to be changed (page 21) The manufacturer states that teriflunomide will not be used in HA and RES populations where fingolimod and natalizumab are more appropriate, however no evidence is provided for the non-HA/RES RRMS population. Given the high proportion of patients with HA or RES in the TOWER trial and the subgroup analyses which suggest teriflunomide is [redacted] in these populations, the effectiveness of teriflunomide in the non-HA/RES RRMS population may be [redacted] in this analysis resulting in an [redacted] of the ICER. However the applicability of the TOWER HA and RES subgroups are unclear given the difference in the definitions of these populations used in this trial.	Alternative wording: The manufacturer states that teriflunomide will not be used in HA despite interferon use and RES populations where fingolimod and natalizumab are more appropriate, however no evidence is provided for the non-HA despite interferon use/RES RRMS population. The TOWER and TENERE studies cannot provide subgroup analyses for HA despite interferon use or RES RRMS because the definitions of these subgroups require MRI measurement at baseline which was not reported within these studies. The only study in which MRI measurement at baseline was carried out was TEMSO and this had a low percentage of overall patients with HAD despite interferon use and RES which were less than 5% (n=10) and 10% (n=33) respectively. This suggests that the impact of removing the results of such a small number of proportion of patients from the overall patient numbers would have a fairly small impact and also it questions efficacy estimates for HA despite interferon use and RES RRMS based on such a small subgroup sample size. Clarification would also need to be provided as to whether data would exist for comparators included within an MTC based on such a non-highly active RRMS definition since most interferon and GA studies are for RRMS patients without a subgroup analysis excluding RES / HAD despite interferon use patients.	In our opinion, it is not appropriate for the ERG to assert that it is possible to estimate the size of the HA despite interferon use and RES RRMS population within TOWER since MRI was not measured in this study and such measurement is needed to define these populations. The study which allows the most accurate estimate of the size of such a population should be used instead (TEMSO) because it did report MRI measurements at baseline and if such an estimate is thought valuable this study should be used to do that. In this regard in the draft SmPC it is worth noting the following wording from Section 5.1: “A consistent treatment effect on relapses and time to 3-month sustained disability progression in a subgroup of patients in TEMSO (n= 127) with high disease activity was observed. Due to the design of the study, high disease activity was defined as 2 or more relapses in one year, and with one or more Gd-enhancing lesion on brain MRI. No similar subgroup analysis was performed in TOWER as no

		MRI data were obtained. No data are available in patients who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or patients having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years.”

Issue 6 Marking of confidential data

Description of problem	Description of proposed amendment	Justification for amendment
Marking of confidential data – some data that is confidential is not marked as such, and vice versa	Page 14, Para 1, lines 2,3 and 5, no longer AIC Page 14, Para 3, lines 1-4, not CIC Page 14, Para 4, lines 1-9, no longer AIC Page 15, Para 1, lines 2-5. Pooled study 2001 /TEMSO most common TEAEs not CIC	Confidential data must be protected. Data in the public domain must not be marked as confidential.

	Page 15, Para 2, lines 1-5, not CIC Page 15, Para 4, lines 3-4, not CIC Page 16, Para 2 Line 4-6, Sentence "..suggest there may be some benefit, results are not statistically significant. There were no clinically meaningful or statistically significant differences in 3 month and 6 month SAD between teriflunomide and Rebif 44µg in TENERE." Should be CIC Page 16, Para 3, Lines 1-3, AND Page 20, Para 1, lines 5-7: Sentence "Overall the treatment benefit of teriflunomide in terms of ARR and 3 month SAD was not reflected in the 6 months SAD results, nor in the change in EDSS over time, ..., none of which demonstrated statistically significant benefit compared with placebo." Should be CIC Page 18, Para 2, line 3, 4, 6 and 8, ICERs should be CIC Page 18, Para 3, lines 3-5, ICERs should be CIC Page 21, Para 4, line 2, ICERs should be CIC Page 21, Para 6, line 3, ICERs should be CIC Page 29: TOWER study design details not CIC (Kappos 2012), TENERE study design details not CIC expect proportion with RRMS, SPMS, PRMS. TEMSO extension study design details not CIC. Page 30, Para 1, lines 4-9. Not CIC. Page 31, Para 1, line 4 use of prior DMT in Phase II and TEMSO not CIC Page 36, meta-analysis RR and 3-month SAD no longer	

	CIC Page 36, Change in EDSS in TEMSO is CIC Page 37, Para 1. Ines 1-3. No longer AIC Page 37, Para 2, line 8. Relapse rate in TEMSO extension (0.206) is CIC Page 38, Para 2, lines 2-4, (TOWER and TEMSO EDSS results) are CIC. Page 40, Para 2, lines 3-7 AND Page 40, Para 4, lines 1-2 AND Page 41, Para 1, lines 5-8 (TENERE trial details) Not CIC. Page 42, Para 2, lines 1-3. Not CIC Page 43, table 9 AND Page 44, Table 10. TENERE Primary outcome, relapse rate, permanent treatment discontinuation, and FIS, treatment satisfaction not CIC Page 44, Para 3, line 1. 3-month and 6-month SAD in TENERE is CIC Page 46, Table 12. TENERE AE data not CIC Page 47, Para 2, lines 2-4. (Common AEs in TENERE) not CIC Page 48, Para 2, lines 2-4. Not CIC Page 54, Table 17, Base case MTC and Direct MA ARR results – no longer AIC Page 55, Table 18. Base case MTC and Direct MA 3mth SAD results – no longer AIC Page 60 Para 5, Line 4 Change in EDSS in placebo	

	controlled studies is CIC Page 60, Para 7. Base case MTC, 3-month SAD no longer AIC Page 61, Para 1, lines 5-8. TENERE discontinuation due to AE, or number previously taking DMT not CIC Page 61, Para 2. Should be CIC Page 74, Table 26 should be CIC Page 78, Table 30 should be AIC Page 82, Table 33 hazard ratio of disease progression for IFN-β 1a (Rebif 22μg) (0.83) should be AIC Page 84, Table 34 hazard ratio of relative annualised rate of relapse for IFN-β 1a (Rebif 22μg) (0.62) should be AIC Page 85, Table 35 should be CIC Page 85, Para 4, line 3 (28.7%) and line 5 (16%) should be CIC Page 86, Table 36 should be AIC Page 89, Figure 13 should be CIC Page 94, Table 41, acquisition costs for Teriflunomide should be CIC instead of AIC Page 98, Para 1, line 1-2, ICERs should be CIC Page 98, Para 2, line 1, QALYs should be CIC Page 98, Para 4, line 5 and line 9, ICERs should be CIC Page 101, Para 3, line 9 ((0.11 vs. 0.57), (0.28 vs. 0.69)), line 13 (0.76 vs. 0.81) and line 14 (0.77 vs. 0.47) should	

	be CIC Page 103, Table 50 should be CIC Page 106, Para 1, lines 9-10, QALYs should be CIC Page 106, Para 2, line 6, QALYs should be CIC Page 106, Para 3, line 7, QALYs should be CIC Page 107, Para 3, line 5, QALYs should be CIC Page 111, Para 1, line 7, ICERs should be CIC Page 111, Para 3, line 3, ICERs should be CIC Page 117, Table 56 should be CIC Page 119, Para 3, line 4 (0.045, 4.5%) should be AIC Page 123, Para 1, line 9, ICERs should be CIC Page 123, Para 2, line 6, ICERs should be CIC Page 125, Para 1, line 4, costs for Teriflunomide should be CIC Page 127, Para 1, line 1, costs for Teriflunomide should be CIC P133, Para 2, lines 4-5. 6-month SAD results are CIC	

Issue 7 Incorrect ICER reported

Description of problem	Description of proposed amendment	Justification for amendment
P18 states: "The ICERs for teriflunomide in the full incremental analysis are reported by the manufacturer as [redacted] per QALY gained compared to Rebif 22µg for the deterministic and probabilistic analyses respectively."	Please change to: "The ICERs for teriflunomide in the full incremental analysis are reported by the manufacturer as [redacted] and [redacted] per QALY gained compared to Rebif 22µg for the deterministic and probabilistic analyses respectively."	To ensure the ERG and AC have the correct information to inform decision making.

Issue 8 There are no patients with PPMS in the teriflunomide studies

Description of problem	Description of proposed amendment	Justification for amendment
Page 29. It states that in TEMSO, TOWER and TENERE studies there were 42, 20 and 2 patients with PPMS (primary progressive MS) respectively. Page 30. It states "However a number of participants have PPMS or SPMS"	For all studies, this should read PRMS (progressive-relapsing MS) and not PPMS.	PPMS is a different type of MS which is characterised by progression from onset without relapses. PRMS is a relapsing form of MS, and is a definition that is more commonly used in the USA and not in the UK.

Issue 9 Incorrect figures in baseline EDSS in teriflunomide studies

Description of problem	Description of proposed amendment	Justification for amendment
Page 30, Para 3, it states: In terms of disease severity all the phase III trials required patients to score 5 or less on the EDSS scale whereas the phase II and extension studies allowed EDSS up to 6, patients with more severe disease	Please change to: In terms of disease severity all the phase III trials required patients to **score 5.5** or less on the EDSS scale whereas the phase II and extension studies allowed EDSS up to 6, patients with more severe disease.	It is important that the baseline characteristics of the studies are correctly reported.

Issue 10 Incorrect baseline characteristics reported

Description of problem	Description of proposed amendment	Justification for amendment
Page 31. Table 2. Not all of the figures are correct.	TEMSO, Mean EDSS reported 2.5, this should be Median EDSS. % White reported 97%. Should be 97.5% (or 98%)	It is important that the baseline characteristics of the studies are correctly reported.

Issue 11 Availability of teriflunomide Draft SmPC

Description of problem	Description of proposed amendment	Justification for amendment
Page 45. It states 'The summary of adverse effects cited the Summary of Product Characteristics (SPC) for Aubagio®, which could not be checked by the ERG as it is not yet available.'	The draft SPC was provided as a reference and as appendix 10.1 in the main submission.	This statement is factually incorrect.

Issue 12 Inaccurate description of most common adverse event class based on extension study data

Description of problem	Description of proposed amendment	Justification for amendment
Page 61 paragraph 2. It states "Extension studies found that hepatic disorders and anaphylactic reactions were the most common class of adverse events". Similar changes need to be made to page 15 paragraph 1 and page 46 paragraph 3	Suggested alternative wording: Extension study data (Comi et al ECTRIMS 2011) found that infections and infestations, hypersensitivity reactions and hepatic disorders (most commonly transient asymptomatic liver enzyme elevations) were the most common class of adverse events.	The existing wording is factually incorrect as shown by the reference cited. The alternative wording is correct. We believe that using the language anaphylactic reactions is misleading unless it is qualified by making clear that this relates to hypersensitivity reactions as is made clear in Table B.6.9.3. page 194 in our submission. Hypersensitivity reactions is the language used in the ECTRIMS poster of the TEMSO extension study data (previously sent).

Issue 13 Cost-effectiveness systematic review search strategy

Description of problem	Description of proposed amendment	Justification for amendment
P63 states: “An important issue is that the manufacturer didn’t adapt the search for Medline, instead they searched Embase and Medline together from the Embase interface. They used the same search and the same methodological filter developed for Embase. The Cochrane Manual advises to adapt the searches to every database.” The search strategy does not need to be adapted for Medline as MeSH terms (associated with Medline) are mapped to Emtree terms (associated with Embase), as stated on the Elsevier website: [Elsevier 2013] “For unique MEDLINE records, index terms assigned by the NLM (which are controlled via the MeSH thesaurus) are mapped to EMTREE terms - making use of the fact that all MeSH terms are included within EMTREE.” As a result appropriate records retrieved from Embase would have also been retrieved from Medline.	Please remove the statement on P63 and recognise that the search strategy does not need to be adapted for Medline.	To ensure the ERG and AC have all available information to inform decision making.

Issue 14 Reference error

Description of problem	Description of proposed amendment	Justification for amendment
P68 states: “Error! Reference source not found” P106 states: “Table Y”	Please update with Figure 5 EDSS state distributions across studies. Please update with Table 52.	To ensure the ERG and AC have the correct information to inform decision making.

Issue 15 Incorrect percentage of relapses leading to hospitalisation reported

Description of problem	Description of proposed amendment	Justification for amendment
P80 states: “Dee et al. estimate that 80% of relapses lead to hospitalisation compared to 69.3% in the TEMSO and TOWER trials.”	Please change to: “Dee et al. estimate that 20% of relapses lead to hospitalisation compared to 30.7% in the TEMSO and TOWER trials.”	To ensure the ERG and AC have the correct information to inform decision making.

Issue 16 Inflation of acquisition costs of beta-interferon and glatiramer acetate

Description of problem	Description of proposed amendment	Justification for amendment
P94 states: “The acquisition costs of	Please remove the statement on P94 and recognise that	To ensure the TAG and AC have the

beta-interferon and glatiramer acetate used in the model are those set by the MS Risk Sharing Scheme and published by the UK Department of Health in 2002.[2] The prices in the model have not been updated for inflation." The acquisition costs for beta-interferon and glatiramer acetate used in the model do not need to be updated for inflation. The acquisition costs are as published in the MS Risk Sharing Scheme by the UK Department of Health until further notice or any updates are provided, of which there have been none [Department of Health 2002].	the acquisition costs of beta-interferon and glatiramer acetate do not need to be updated for inflation.	correct information to inform decision making.

Issue 17 Incorrect QALYs reported

Description of problem	Description of proposed amendment	Justification for amendment
P104 it states: “The QALYs in TA 32 range from 8.93 to 9.57 and the cost from £68,453 to £102,133.”	Please change to: “The QALYs in TA 32 range from 8.93 to 9.95 and the cost from £68,453 to £131,455.”	To ensure the TAG and AC have the correct information to inform decision making.

Issue 18 Incorrect change in ICER reported

Description of problem	Description of proposed amendment	Justification for amendment
P123 it states: “They found that a 25% decrease in efficacy after 5 years increased the ICER compared to the blended comparator by £4,000 per QALY, and a 50% decrease increased it by £8,000 per QALY.”	Please change to: “They found that a 25% decrease in efficacy after 5 years increased the ICER compared to the blended comparator by ~£4,000 per QALY, and a 50% decrease increased it by ~£8,000 per QALY.”	To ensure the TAG and AC have the correct information to inform decision making.

Issue 19 Accurate heading of ICER tables

Description of problem	Description of proposed amendment	Justification for amendment
Pages 129 and 131, Tables 70,76, a need for clarity of what ICER results being described	Add asterisk to ICER column as in “ICER*” and under tables put the wording - *ICERs are comparing comparators to teriflunomide with the exception of the ICER in the teriflunomide row which is vs glatiramer acetate.	Provide clarity as to what the ICERs are providing

Issue 20 Accurate heading of ICER tables

Description of problem	Description of proposed amendment	Justification for amendment
Page 130, Tables 72,74, need for clarity of what ICER results being described	Add asterisk to ICER column as in "ICER*" and under tables put the wording - *ICERs are comparing comparators to glatiramer acetate.	Provide clarity as to what the ICERs are describing

Issue 21 Mistake in estimation of ICERs

Description of problem	Description of proposed amendment	Justification for amendment
Page 128, Table 68 ICER for preferred ERG analysis looks to be wrong. For example Rebif 22 ICER if versus GA should be £285,580. If versus teriflunomide Rebif 22 dominates. Stated ICER is £47,463.	Clarify what the ICER is comparing (unclear from table) and correct values presented.	Accuracy and clarity.

References

Comi et al. Extension of a Phase III trial (TEMSO) of oral teriflunomide in multiple sclerosis with relapses: safety outcomes with up to 4 years of follow-up

Department of Health (DH). *Cost effective provision of disease modifying therapies for people with multiple sclerosis*; 2002. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012214.pdf

Elsevier. Embase Training and Support. Accessed August 2013. http://www.elsevier.com/online-tools/embase/training-and-support

(please cut and paste further tables as necessary)