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[redacted]

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8th October 2013

Dear Members of Technology Appraisal Committee B,

Re: NICE Appraisal Consultation Document: Teriflunomide for treating relapsing-remitting multiple sclerosis

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:
    - 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

- The use of a cost-effectiveness model that incurs greater benefits for therapies that have a higher discontinuation rate, which favours teriflunomide over fingolimod
- 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.
- 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*

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Section A: Main Comments on the ACD

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) First-line Use of Fingolimod

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 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) Subgroup Considerations

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) Data Limitations

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.

Conclusion on Comparisons Reported in the ACD

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.**

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.

Section B: Additional Comments on the ACD

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) Concern over the ERG's Economic Analysis in Patients with Highly Active RRMS

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].

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) Disability Progression

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)

Table 1: 24-week sustained disability progression at 24 months

	Teriflunomide(3)	**Fingolimod(2)**
	14mg	**0.5 mg**
Reduced risk over placebo	25.1%	37%
P value	0.1259	0.01

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) Adherence Rates

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 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) Long-term Outcomes

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.

Section C: Consistency with Previous Technology Appraisals

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].

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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.

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Issue 1 Impact of treatment discontinuation rates (critical point)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
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.	We propose that the model should be re-run with the same discontinuation rate applied to all treatments as the base case.	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

Issue 2 Monitoring costs attributable to fingolimod

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
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	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	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

with common practice		the deterministic results (to 6 decimal places) and potentially warrants further investigation.

Issue 3 Model parameters for PSA

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
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	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.	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.