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Date	August 25th 2011
Division/Dept.	[redacted]
Care of	[redacted]
Phone	[redacted]
Fax	[redacted]
E-Mail	[redacted]

Our ref. **Multiple sclerosis (relapsing-remitting) - fingolimod: appraisal consultation document**

Dear Jeremy,

Merck Serono has reviewed the Appraisal Consultation Document (ACD) for fingolimod in relapsing-remitting multiple sclerosis and given the incomplete submission of evidence for all patient sub-groups considered, support the preliminary recommendation of the Appraisal Committee.

As noted in the ACD, there are few treatment options for people with rapidly evolving severe relapsing-remitting multiple sclerosis and we agree with the clinical specialists consulted that this assessment marks a missed opportunity to recommend an additional treatment option for this patient group. A further assessment following this appraisal might be appropriate and would allow consideration of fingolimod to be used where it is likely to provide most benefit.

Unfortunately the ERG critique highlights that the economic model developed for this submission is not fit for purpose. It is therefore not possible to reconsider this preliminary recommendation by simply re-assessing cost effectiveness following the adjustment of input variables. A positive change in the preliminary recommendation would require a complete re-assessment with a validated model that most importantly included consideration of all relevant comparators.

Registered Office and Principal Place of Business

Merck Serono Limited
Bedfont Cross, Stanwell Road
Feltham, Middlesex
TW14 8NX
United Kingdom

Phone + 44 (0)20 8818 7200
Fax + 44 (0)20 8818 7267
www.merckserono.co.uk

Registered in England Number 990823

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Please find below our specific comments:

1. ***Has all of the relevant evidence been taken into account?***

We do not believe all of the relevant evidence has been taken into account for this appraisal, notably:

- Paragraph 4.5: Adverse effects

Comments: In accordance with the marketing authorisation conditions and restrictions for the supply of fingolimod, as detailed in the Gilenya EPAR issued by the EMA, fingolimod is subject to a comprehensive risk management plan.

Evidence of further serious adverse events associated with fingolimod are emerging including delayed asystole (Espinosa, Multiple Sclerosis 2011), complete heart block (Jones, CMSC 2011), retinal vein occlusion (Gallego-Pinazo, Journal of Neuro-Ophthalmology, 2011) and six cases of malignancy reported during the extension phase of the TRANSFORMS trial (Khatri, Lancet Neurology, 2011).

Further consideration of the monitoring and treatment economic burden associated with fingolimod use may be warranted. In particular, the 18.4% of patients in the FREEDOMS and TRANSFORMS trials who developed grade 4 lymphopenia (Francis, ECTRIMS 2010) which usually requires urgent intervention, and the 12.4% of patients who did not recover from the first dose bradycardia within 6 hours and required additional monitoring, of which 14% required hospitalisation (DiMarco, ECTRIMS 2010).

2. ***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?***

- Paragraph 3.16: Definition of different populations

Comments: While it is noted that there is considerable overlap between the populations defined in the marketing authorisation for fingolimod, in fact, it should be acknowledged that population 1a in this appraisal is actually a subset of the much larger population 1b.

- Paragraph 3.17 & 4.8: Statistical power

Comments: As noted by the ERG, the estimated efficacy (relative effect) of fingolimod in the population sub-groups as defined by the marketing authorisation and considered in this appraisal is questionable as these populations are different (less than 50%) of the total trial population.

- Paragraph 4.6: Relevant comparators

As noted by the Appraisal Committee, the submission does not consider the range of possible treatment alternatives as listed in the final scope.

- Paragraph 4.17: Core issues with the cost effectiveness assessment

As summarised in 4.17 the base case ICER for fingolimod is unreliable. We agree with the Appraisal Committee assessment which concludes a more plausible ICER is likely to be significantly higher than £55,600.

In addition, we also note the ERG quality assessment of the economic model (Evaluation Report, Appendix 1) which highlights issues as follows:

  - The structure of the model is not consistent with a coherent theory of the health condition under evaluation: while it appears consistent with previous models, it does not seem coherent with the clinical observations of progression resulting as a consequence of relapse;
  - The causal relationships described by the model structure are not justified appropriately: 50 year time horizon used in the model compared to 20 years used in previous models;
  - All feasible and practical treatment options have not been evaluated: other treatment options have been overlooked;
  - Time horizon of the model, duration of treatment and treatment effect: duration of treatment and treatment effect is not justified;
  - Questions have been raised about whether RRMS and SPMS progress in the manner modeled;
  - Questions have been raised about the transparency of the data used to populate the model and its conversion for use within the model;
  - Particular attention has not been paid to identifying data for important parameters within the model: no systematic review was conducted;
  - Modelling assumptions were not justified;
  - No justification has been provided for the extrapolation of short term trial data over 50 years – important as is different to previous NICE assessments of DMT's;
  - The principal types of uncertainty have not been addressed.

It is important to recognise that given the depth of the issues identified with the economic evaluation, it would not be possible to change the preliminary recommendation by re-assessing cost effectiveness following the adjustment of input variables. The ERG critique highlights that the model is not fit for purpose. Any change in the preliminary recommendation would require a new assessment with a validated model that most importantly included consideration of all relevant comparators.

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3. ***Are the provisional recommendations sound and a suitable basis for guidance to the NHS?***

The provisional recommendation is sound and constitutes a suitable base for the preparation of guidance to the NHS.

Sincerely,

[redacted]

[redacted]