18 December 2006

[redacted]

Dear [redacted]

Single Technology Appraisal - Natalizumab for Multiple Sclerosis

The Evidence Review Group, Peninsula Technology Assessment Group at the University of Exeter (PenTAG), and the technical team at NICE have now had an opportunity to take a first look at the industry submission document and economic model submitted by Biogen Idec. There are a number of issues and queries on which we are seeking your feedback at this early stage.

The comments and queries included in this letter are divided into three sections:

- **Clinical evidence**
  This section outlines points relating to the clinical evidence presented in your submission which will improve our understanding of the evidence base.

- **Cost effectiveness**
  This section lists queries relating to the cost effectiveness modelling which will improve our understanding of the model inputs and outputs.

- **Textual clarifications and additional points**
  This section requests clarification in relation to the text of the submission, which may have an impact on the validity of evidence presented on clinical effectiveness and cost-effectiveness.

Both PenTAG and the technical team at NICE will be addressing these points in their reports. As there will not be any consultation on the evidence report prior to the Committee Meeting you may want to do this work and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by the end of Tuesday 9th January 2007.
Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

If you present data that is not already reference in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

We will need to come back to you in due course to discuss the commercial and academic in confidence information in your submission. The Institute seeks to be as transparent as possible in its decision making and I encourage you to consider how the amount of confidential information in your submission could be reduced.

Yours sincerely

Meindert Boysen, *Pharmacist MScHPPF*
Associate Director – Single Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clinical evidence

A1. Please provide details of the results of disability progression in the AFFIRM trial as measured by the MS functional composite scale.

A2. Please provide data on the number of relapses per year seen in Table 2 for the combined group of people with two, and people with more than two relapses in the year prior to screening.

A3. Please provide any interim data available about adverse events with natalizumab from the 101-MS-321/322 and TYGRIS 101-MS-403 trials described in Table 4.

A4. Please provide more detail about how and why the adverse event data for natalizumab was pooled (page 89).

A6. Please provide the data from the meta-analyses that were used to inform the indirect comparisons. We note that the Cochrane review presents a 'best' and 'worst scenario' for individual comparisons. Please provide indirect comparisons that use these sensitivity analyses.

A7. Please provide details of the patient baseline characteristics and clinical results from the SENTINEL trial.

Section B: Cost Effectiveness

B1. Please provide the "in press" UK MS survey by Orme et al (reference 14).

B2. Please provide a copy of the cost data by disease severity from Tyas et al (reference 143).

B3. Please provide the London Ontario dataset used in the model.

The Evidence Review Group has requested that the information outlined in sections B1 to B3 be sent to the Institute as early as possible prior to the deadline of Tuesday 9th January.

B4. Given the use of AFFIRM to model the natural history of MS in the model, please explain why the treatment arm was not used to derive transition probabilities for the natalizumab group.

B5. Please explain why your indirect comparison data is not used in the model.

B6. In the listing of the one-way sensitivity analyses on page 158, it is unclear how progression data has been altered. Please provide more detail on this.

B7. Please confirm whether one-way sensitivity analyses were carried out on costs of natalizumab and death rates, as they do not appear to be reported.

B8. Please provide the results of multi-way sensitivity analyses that you suggest on page 156 – 6.3.3.1 first sentence – are included in table 85 but do not seem to be included.

Section C: Textual Clarifications and additional points

C1. Please explain what the asterisk in the key under Table 8 refers to.

C2. Please check whether there is a mistake in Table 27 on page 78. Should the correct figures read 79/124 for INFB MS Group and 257/466 in the total column underneath? Please confirm whether or not these are mistakes and whether this has affected any calculations.

C3. Please explain the meaning of "a high proportion of data in early EDSS states has been imputed" (Academic in Confidence, penultimate paragraph, page 94).

C4. Page 101 states that the questionnaire for the MS survey is provided in Appendix J but this appears to be missing. Please provide this appendix.

C5. Some data in the model are labelled as being informed by the "1801 trial". Please clarify whether this is the AFFIRM trial.

C6. Please provide a list of the external experts and how they contributed to the submission, and outline the contractual agreements made.